

ANATOMY AND HISTOLOGY

- Liver is the largest organ in the human body (1-1.5 kg)
- Occupies the upper right abdomen and epigastrium and hold in place by ligamentous attachments to diaphragm.
- The liver receives approximately 30% of resting cardiac output and is therefore a very vascular organ.

Receives dual blood supply:

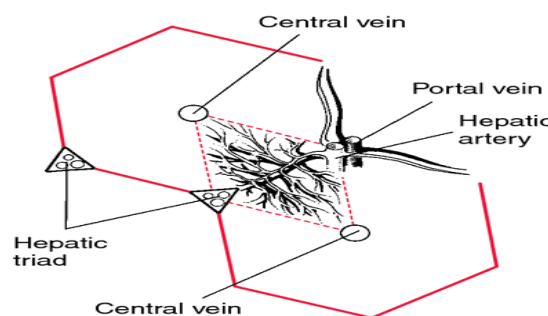
20% = hepatic artery: oxygen rich

80% = portal vein: nutrient rich

Venous drainage: through the hepatic veins to the IVC

Hepatic lobules (physiological unit of liver):

- ✓ Most livers have between 50,000 and 100,000 lobules.
- ✓ Each lobule consists of a central vein surrounded by tiny liver cells grouped in sheets or bundles. Cavities known as sinusoids separate the groups of cells within a lobule.
- ✓ The hepatic artery and the portal vein branch into a network of tiny blood vessels.
- ✓ The sinusoids drain into the central veins, which join to form the hepatic vein. Blood leaves the liver through the hepatic vein to the IVC
- ✓ Each lobule also contains bile canaliculi (ductules) carry the bile secreted by the liver cells, join to form bile ducts, which carry bile out of the liver.
- ✓ Bile from the liver and gall bladder secreted into the small intestine through the common bile duct



Formation of Lymph in the Liver:-

Approximately half of the lymph formed in the body is formed in the liver. Due to the large pores or fenestrations in sinusoidal endothelial cells, fluid and proteins in blood flow freely into the space between the endothelium and hepatocytes (the "space of Disse")

The hepatic phagocytic system:

Kupffer cells lie beneath the endothelial lining of sinusoids and have phagocytic activity against bacteria, virus, and immune complexes.

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PHYSIOLOGY**1- Protein metabolism:**

- Synthesis of plasma proteins (albumin- alpha & beta globulin) & co-agulation factor & urea from ammonia
- Metabolism of amino acids

2- Carbohydrate metabolism:

Maintain the blood glucose level within normal as

- After feeding : glycogenesis & lipogenesis (storage of glucose)
- During fasting: glycogenolysis & gluconeogenesis.

3- Lipid metabolism

- Synthesis, esterification & excretion of cholesterol.
- Synthesis & degradation of triglycerides.
- Synthesis of lipoproteins.

4- Bile salts metabolism

- Synthesis (from cholesterol) then Excreted to be returned in Enterohepatic circulation.

5- Detoxification of drugs & toxins**6- Endocrinal functions**

- Catabolism of hormones.
- Production of smatomedins, angiotensinogen & erythropoietin.
- Production of hormone-binding proteins.
- Activation of vitamin D.

8- Hematopoietic functions: During fetal life & in certain diseases.**9- Immune functions:** (as phagocytic activities)**10- Bile pigments metabolism:** (See jaundice)

LIVER FUNCTION TESTS

I. Synthetic function	II. Excretory	Liver damage (enzymes)	III. Metabolic	others
1. Plasma proteins 2. Prothrombin	• Total bilirubin • Direct bilirubin • Indirect bilirubin	• ALT • AST • Alkaline phosphates • GGT • 5 Nucleotidase	• Cholesterol level • Glucose tolerance test	Alpho feto protein (AFP)

I. Synthetic function**1. Plasma proteins:**

- Total protein: 6-8 gm/dl
- Albumin: 3.5-5.5 gm/dl
- Globulin: 1.7-2.7 gm/dl
- A/G ratio: 2/1

Albumin is synthesized by liver only, and it has a long half life so affected in chronic liver disease and A/G ratio may be reduced (1/2)

2. Prothrombin: P.T. = 12-14 sec.

Only synthesized by liver depending on vit.k & has a short half life so affected in acute or chronic liver disease

I.N.R = international normalization ratio

= patient prothrombin T./ normal prothrombin = 0.8-1.2

- **Used in monitoring patient on oral anticoagulant**

II. Excretory

- Total Bilirubin < 1mg/dl ($\uparrow$ in all types of jaundice)
- Direct Bilirubin < 0.2 mg/dl ($\uparrow$ in obstructive jaundice)
- Indirect Bilirubin < 0.8 mg/dl ($\uparrow$ in hemolytic)

N.B.: Both are elevated in hepato cellular jaundice

III. Liver damage

1. SGOT (AST)	2. SGPT (ALT)
- 7-40 Iu/l - Mitochondrial - Not specific - Short half life (early recovery) - Elevated with alcoholic.	- 7-40 Iu/l - Cytoplasmic - Specific - Long half life

only in alcoholism AST/ALT > 2/1

- Markedly elevated in acute hepatitis or necrosis (shooting up > 10 folds)
- Around 3-4 folds in chronic liver diseases
- Normal or subnormal in advanced liver diseases

3. Alkaline phosphates (ALP)**Origin**

Endothelium of bile duct & cell wall of hepatocytes

3-13 KAU (king Armstrong unit)

Markedly elevated in:

- Biliary obstructive (O.J.)
- Space occupying lesions
- Bone diseases

Not specific so specification by GGT is important.

4. Gamma Glutamyl trans peptidase (GGT)

Elevated in liver diseases, not in bone diseases

5. 5 Nucleotidase: specific**IV. Metabolism****Fat:**

- S. cholesterol = 150-200 mg %
- In O.J. → hyper cholesterolemia
- In L.C.F. → normal cholesterol & decreased estrification

CHO:

- In cute liver diseases → hypoglycemia
- In chronic liver diseases → Impaired GTT

V. Others

- As:**
- Hepatitis markers
 - Alpha feto protein (AFP)

Hepatitis

A) Acute hepatitis:

1. Infection:

- Viral hepatitis
- CMV, herpes simplex, EBV, yellow fever.

2. **Drugs & toxins:** Alcohol, halothane, isoniazid & paracetamol.

3. **Metabolic:** Wilson's disease.

B) Chronic hepatitis:

- Chronic active hepatitis
- Chronic persistent hepatitis.
- Chronic lobular hepatitis

Viral hepatitis

Aetiology:

- Common hepatotropic viruses: HAV, HBV, HCV, HDV, & HEV.
- Other viruses: G, GB and TT viruses, CMV, herpes simplex, EBV and yellow fever virus.

Virology

	HAV	HBV	HCV	HDV	HEV
Genome	RNA	DNA	RNA	RNA	RNA
Transmission	Faecal-oral	Parenteral Sexual Vertical	Parenteral	parenteral Sexual Vertical	Faecal-oral
Epidemics	May be	No	No	No	May be
Incubation Period	2-6 weeks	2-6 months	2-6 months	2-6 months	2-6 weeks
Severity	Mild	Mild or Severe	Mild	Mild or severe	Mild
Chronicity & Liver cancer	No	May be	Usually	May be	No
Carrier state	No	+ve	+ve	No	No
Prophylaxis	Hygiene Igs HA vaccine	Hygiene, HBIG, HB vaccine	Hygiene	Hygince HB vaccine	Hygiene

ACUTE HEPATITIS

Pathological changes:-

- Evidence of hepatocytes degeneration (ballooning) and apoptosis (acidophilic bodies called the Councilman body)
- Evidence of inflammation (lobular and portal mononuclear infiltrate.
- More severe cases demonstrate bridging necrosis.
- Because there is usually preservation of the reticular framework, the liver completely restores itself with hepatocyte regeneration.
- Liver biopsy is not generally helpful in distinguishing between the different types of acute hepatitis, as the histology is quite similar.

Clinical Picture:

The clinical presentation is variable in severity and includes:-

1. Asymptomatic cases
2. symptomatic :
 - ✓ Anicteric hepatitis
 - ✓ Icteric hepatitis
 - ✓ Complicated as fulminant hepatitis

A) An-icteric Hepatitis:

1. These are mild cases without jaundice.
2. The condition presents by influenza-like or GIT symptoms
3. It is usually missed in diagnosis

B) Icteric Hepatitis: (Passes through 3 stages)

1. Pre-icteric stage: (3 days up to 2 weeks)

- Symptoms:

- Acute onset of fever, headache & malaise
- Anorexia is marked especially towards cigarettes & alcohol
- There may be nausea, vomiting & abdominal distension
- Dull aching pain in right hypochondrium & epigastrium.

- Signs:

- Fever with relative bradycardia
- The liver is enlarged, soft, smooth & tender.
- Non-specific rash & neck rigidity may occur especially in children.

2. Icteric stage: (1-4 weeks)

- Symptoms:

- Jaundice appears with drop of fever & improvement of the condition of the patient.

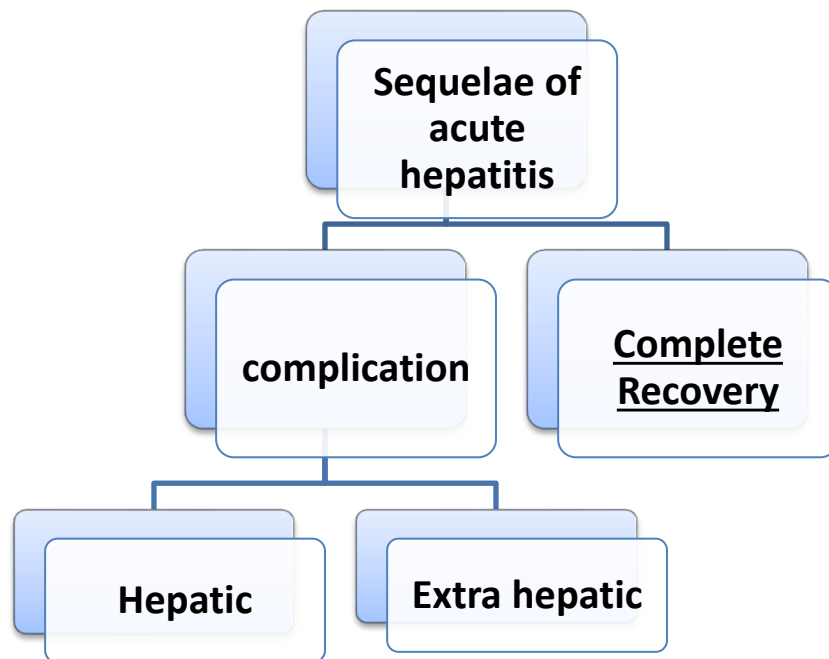
- Darkening of urine occurs at first followed by lightening of stools & then scleral icterus.
- Anorexia, nausea & vomiting usually diminish or disappear
- Pruritus may occur.

- **Signs :**

- The liver is enlarged, soft, smooth & tender
- The spleen is mildly enlarged in 20% of cases
- Lymph nodes in the posterior triangle may be enlarged.

3. Convalescence stage (post-icteric):

- There is gradual improvement of symptoms & signs
- Complete clinical, biochemical & histological recovery of the liver may take up to 6 months.



I. Hepatic Complications

1. *Relapses (biphasic) hepatitis:*

The original attack recurs in biochemical abnormalities (rise of serum bilirubin & enzymes)

2. *Fulminant Hepatitis:* (Massive hepatic necrosis)

- ✓ It is a rare form, manifested by acute liver failure
- ✓ May develop so rapidly that jaundice is not apparent & condition may be misdiagnosed as encephalitis or psychosis.
- ✓ Death may occur from infection, hypoglycemia, increased intracranial pressure with cerebral edema or renal failure.

3. Cholestatic Hepatitis: commonly with HAV

Prolonged course of cholestatic features e.g. pruritus, dark urine, light stools with fall in the aminotransferase but with an increased alkaline phosphatase value..

4. Post-Hepatitis Syndrome:

Presents with fatigue, failure to regain weight, anxiety, anorexia & abdominal discomfort

✓ Liver function & biopsy normal with mild elevated enzymes.

5. Chronic Sequelae: 4 Cs (only in cases of HBV, HCV & HDV)**1. Chronic hepatitis:**

- Chronic active hepatitis
- Chronic persistent hepatitis
- Chronic lobular hepatitis

2. Cirrhosis**3. Carcinoma****4. Carrier state****II- Extra-hepatic Complications (AGPC)**

- Arthritis & Arthralgia & Aplastic anaemia
- Pancreatitis & Poly arteritis nodosa
- Cryoglobulinaemia (mainly with HCV)
- Glomerulonephritis (usually with HBV)
- Guillain-Barre syndrome
- Others : Urticaria & skin rash, myocarditis

Investigations:**1. Liver Function Tests:**

- Serum bilirubin is increased (biphasic)
- Transaminases are markedly increased (shooting up)
- Alkaline phosphatase is moderately increased
- Gamma globulins are increased
- Prothrombin time defines the extent of liver injury in the acute stage, as implying a poor prognosis.

2. Hepatitis Markers:**Hepatitis A markers:**

Anti-HAV antibodies: - IgM Denotes recent infection
- IgG denotes previous infection

HAV Ag in stools (rarely used)

Hepatitis B markers:

HBsAg (surface Ag)	Appears in blood about 6 weeks after infection & disappears after 3 months. Persistence for > 6 months indicates a carrier or chronic state.
Anti-HBs	Appears after 3 months & persists. It accounts for recovery & immunity with IgG
HBcAg(core Ag)	It is not detected in blood but in liver biopsy
Anti-HBc (IgM & IgG)	IgM = recent infection IgG = old infection
HBeAg (pre-core Ag)	Indicates infectivity & its persistence indicates ongoing chronic disease.
Anti-HBe	Indicates low infectivity.

HBV, DNA: by **PCR** it is the most sensitive indicator of viral replication

Hepatitis C markers:

Anti-HCV antibodies: by ELISA or RIBA detected after 5-6 weeks of infection.

HCV, RNA: by PCR detected after 2 weeks of infection.

Hepatitis D markers:

- Anti-HDV antibodies:
 - IgM denotes recent infection
 - IgG denotes previous infection
- HBsAg is positive.
- HDV, RNA: by PCR.

Hepatitis E markers:

- Anti-HEV antibodies:
- IgM denotes recent infection
 - IgG denotes previous infection

3. Liver Imaging: e.g. abdominal ultrasound may show bright enlarged liver.

4. Blood Picture: Leucopenia with relative lymphocytosis

5. Urine Analysis:

- Bilirubin & bile salts are present
- Urobilinogen is variable
- There may be slight proteinuria

6. Stool Analysis:

- Pale Stools and may be features of steatorrhoea.
- Decreased stercobilinogen

Treatment:

1. Rest: is advised until the patient becomes symptom-free, the liver is no longer tender & serum bilirubin is less than 1.5 mg/dl

2. Diet:

- High-carbohydrate & protein diet is given.
- Proteins should be restricted if manifestations of liver failure appear.
- Low-fat diet is usually preferred if nausea is marked.
- Alcohol should be avoided during the disease (at least a year after)

3. Symptomatic treatment: e.g.

- Antiemetics e.g. domperidone for nausea & vomiting
- Cholestyramine for pruritus

4. Treatment of complications:

- e.g. steroids may be used in cholestatic hepatitis

Prevention

1. General :- Public health & hygienic measures

2. Immunoglobulins are given to exposed individuals as soon as possible after exposure.

3. Vaccines:-

HBV vaccine:

It is given to groups at high risk for HBV infection including:

- Health professionals e.g. surgeons, dentists, laboratory workers,
- Patients requiring repeated transfusions e.g. haemophiliacs
- Haemodialysis patients.
- Household contacts of HBV patients.
- Babies born to HBsAg-positive mothers.
- May be given to all children in high-risk areas.
- Homosexuals.
- IV drug abusers.

It gives an effective protection for about 5 years.

The vaccine is formed of HBsAg prepared by recombinant DNA technology.

Hepatitis A vaccine: should be given to individuals in high-risk areas.

CHRONIC HEPATITIS

Def : hepatitis lasting more than 6 months

Old histological classification

1. Chronic active hepatitis
2. Chronic persistent hepatitis
3. Chronic lobular hepatitis

CHRONIC ACTIVE HEPATITISAetiology:***

Viral	Hepatitis B, C, D
Nonviral	1. Autoimmune 2. Drugs:- Isoniazid – L.dopa – Nitrofurantoin – Acetaminophen 3. Alcoholic hepatitis – Nonalcoholic steatohepatitis 4. Rare:- α_1-antitrypsin deficiency or Wilson's disease

Pathology

<u>1. Mild Form:</u>	<u>2. Severe Form</u>
♦ Infiltration of inflammatory cells is limited to the portal tracts (mononuclear cells) ♦ The inflammation & necrosis extend into the hepatic lobules with erosion of the limiting plate (<u>Piecemeal necrosis</u>)	♦ In addition to the previous features there are <i>fibrous septa extending</i> into the hepatic lobules with isolation of groups of liver cells in the form of rosettes. ♦ <u>Bridging necrosis & fibrosis</u>, either portal-central or portal-portal, are seen. Then progress to cirrhosis.

Recent scoring system:

	Pathology
0	- None or minimal portal inflammation
1	- Portal and/or lobular inflammation without necrosis
2	- Mild limiting plate necrosis (mild interface hepatitis) and/or focal lobular necrosis
3	- Moderate limiting plate necrosis (or moderate interface hepatitis) and/or severe focal cell necrosis (confluent necrosis)
4	- Severe limiting plate necrosis (or severe interface hepatitis) and/or bridging necrosis.

	Viral	Autoimmune
Clinical Picture	Patient at high risk as drug addict or homosexuals	Common in young adult females
	Patients with chronic liver disease may present in a number of 3 ways: 1. <u>Asymptomatic</u> :- only abnormal liver function tests persisting for at least 6 months. 2. <u>Symptoms of chronic liver disease</u> Non-specific: as fatigue, food intolerance, anorexia, abdominal discomfort Specific as pain in the right hypochondrium, jaundice (mild) but late, features of cirrhosis may present with a complication related to portal hypertension such as ascites or a variceal bleed or liver cell failure. 3. <u>An episode of acute hepatitis</u> (The least frequent presentation) Signs: - The liver is enlarged, firm & tender but later may be shrunken - The spleen is usually enlarged - Signs of liver failure (e.g. jaundice, ascites, oedema & encephalopathy) are late features.	
Investigations	History of hepatitis-drug abuse-blood transfusion-sexual promiscuity Extra-hepatic manifestation mainly with HCV may be present (see above)	An associated other autoimmune disorders (e.g. RA, thyroiditis, vasculitis polyarthritis, pneumonitis, autoimmune hemolytic anemia & proliferative glomerulonephritis)
	1. Liver function tests: - Serum bilirubin is increased (biphasic) - Transaminases may be markedly elevated & alkaline phosphatase is moderately elevated. - Albumin may decrease & globulins increase. - Prothrombin time is prolonged 2. Liver imaging : e.g. abdominal ultrasound 3. Liver biopsy is diagnostic (see histological staging)	
	Hepatitis markers (for B, C & D viruses)	Typ 1=Antinuclear, antismooth muscle Type 2 = Anti-LKM antibodies,

Treatment	<u>For chronic active HBV :-</u> Interferon and/or oral antiviral drugs (Entecavir, Adefovir, Lamivudine & Telbivudine)	1. Prednisolone: High-dose 40-60 mg/day for 4-6 weeks, the gradually reduced to a maintenance dose 5-10 mg/day for 6 months to 3 years according to the response.
	<u>For chronic HCV:-</u> Interferon as a single regimen or combined with Ribavirin	2. Azathioprine (Imuran): 50-100 mg/day may be added to prednisolone to potentiate its effect & reduce its dose.
	Hepatic transplantation: may be considered in the late stages of the disease.	

Alpha-Interferon (IFN- α):-

Dose: 3 million units in HCV and 10 million units in HBV SC three times a week for at least 6 months.

Response occurs in about 50% of patients. When the drug is stopped

Side effects – Early : flu-like symptoms, fatigue, diarrhea. Late: depression, BM suppression.

Peg- Interferon: used once /week with a higher rate of response and lesser side effects than ordinary interferon.

Disease activity in HBV:

Chronic active disease	Inactive HBsAg carrier state
- HBsAg positive > 6 months - Serum HBV DNA > 100,000 copies per mL - $\pm$ elevation of ALT - Liver biopsy showing chronic hepatitis (score $\geq$ 4)	- HBsAg positive > 6 months - HBeAg negative, anti-HBe positive - Serum HBV DNA < 100,000 copies per mL - Normal ALT - Liver biopsy to confirm absence of significant hepatitis (score < 4)

Criteria suggestive for autoimmune diseases:

- The presence of serologic immune markers
- An association with HLA common in autoimmune disorders
- A predominance of T lymphocytes and plasma cells in liver histologic lesions
- Complex vitro defects in cellular immunity and immunoregulatory functions
- An association with other autoimmune disorders
- A response to therapy with corticosteroids or immunosuppressants

Overlap syndromes: features of both autoimmune hepatitis and another chronic liver disorder (eg, primary biliary cirrhosis, chronic viral hepatitis).

Chronic persistent hepatitis**Aetiology:**

1. Viral hepatitis (B, C & D viruses) 2. Drugs & toxins as alcohol

Pathology:

There is expansion of the portal tracts due to inflammatory infiltration by mononuclear cells. There is no piecemeal necrosis, rosettes or bridging. Progression to chronic active hepatitis or cirrhosis is rare.

Clinical Picture:

- Usually asymptomatic.
- Non-specific symptoms as fatigue, food intolerance, anorexia, abdominal discomfort.
- Hepatic manifestations as pain in the right hypochondrium ± mild jaundice.

Signs:

- Liver may be mildly enlarged -tender& spleen may be slightly enlarged

Investigations:

1. Liver function tests:
 - Serum bilirubin is normal or slightly elevated.
 - Transaminases may be moderately elevated
2. Liver imaging: e.g. abdominal ultrasound.
3. Liver biopsy is diagnostic
4. Investigations for the cause: e.g. hepatitis markers.

Treatment: Reassurance of the patient & Avoidance of hepatotoxins

LIVER CIRRHOSIS

Definition: Pathological changes characterized by degeneration followed by fibrosis and regeneration leading to irreversible loss of normal hepatic architecture.

Etiology:

1. Alcoholic cirrhosis (leannec's cirrhosis)
2. Billiary cirrhosis
3. Chronic hepatitis (post hepatitis cirrhosis)
4. Cardiac cirrhosis
5. Cryptogynic (idiopathic) cirrhosis
6. Drugs: Methotrexate, INH, Methyldopa, Amidodarone
7. Metabolic:
 - Hemochromatosis ($\uparrow$ Fe)
 - Hepatolenticular degeneration ($\uparrow$ Cu)
 - α 1 antitrypsin deficiency
8. Miscellaneous:
 - Severe malnutrition
 - Sarcoidosis

Inherited cirrhosis:-

- Cystic fibrosis.
- Alpha-1 antitrypsin deficiency.
- Galactosaemia.
- Glycogen storage diseases.
- Wilson's
- Haemochromatosis

Classification

A) Aetiological:- (as above)

B) Morphological:-

1. Micronodular Cirrhosis:

Regeneration nodules are small (< 3 mm) and of the same size.

2. Micronodular Cirrhosis:

Regeneration nodules are big (< 3 mm) and of variable size

3. Mixed Cirrhosis:

C) Functional:-

1. Compensated (Latent) Cirrhosis.

2. Decompensated (Manifest) Cirrhosis.

Clinical picture

A) Compensated (Latent) Cirrhosis:

The condition may be asymptomatic & accidentally discovered during evaluation of unrelated condition e.g. by detection of hepatomegaly during abdominal examination or imaging.

B) Decompensated (Manifest) Cirrhosis:

1. Parenchymatous (cellular) decompensation = manifestations of **liver failure**.
2. Vascular decompensation = manifestations of **portal hypertension**.
3. Features of the cause: - usually specific
4. Complications: -
 - a. Hepatocellular carcinoma.
 - b. Infections e.g. spontaneous bacterial peritonitis & bacteraemia.
 - c. Increased incidence of peptic ulcer.
 - d. Increased incidence of gallstones.
 - e. Impaired glucose tolerance & rarely diabetes mellitus.
 - f. Portal vein thrombosis.

Local abdominal examination:

1. Liver is firm with sharp border & usually shrunken.
2. Splenomegaly, dilated veins on abdominal wall & ascites may be present.

Investigations

A) Diagnosis of cirrhosis with (cellular and vascular evaluation)

Liver function tests: (features of chronic liver diseases)

- Plasma proteins: decreased albumin, increased globulins and A/G ratio is decreased & may be reversed.
- Prothrombin time: prolonged & not corrected by IV vitamin K.
- Serum bilirubin: increased (biphasic).
- Transaminases & alkaline phosphatase are moderately elevated.

Liver imaging: e.g. abdominal ultrasound, CT scan & isotopic scanning.
(Irregular surface, attenuated hepatic vein +/- changed texture)

Liver biopsy: the only conclusive.

Investigations for portal hypertension: (see portal hypertension)

B) Detection of complications:

Tumour markers of hepatocellular carcinoma: e.g. Alpha fetoprotein

C) Detection of the cause: Usually specific

Patients with cirrhosis, on top of HBV, HCV or haemochromatosis, should be screened for hepatocellular carcinoma (α -fetoprotein and abd. Ultrasound every 6 – 12 months)

Treatment**1. Treatment of complication of cirrhosis including:**

- Treatment of liver failure.
- Treatment of portal hypertension.
- Treatment of hepatocellular carcinoma.

2. Supportive:-

- Antifibrotic drugs (e.g. colchicines) are of doubtful value.
- Liver support by multivitamins and essential amino acids.

3. Hepatic transplantation: it is the only curative treatment & should be considered in patients with end-stage liver disease.

4. Treatment of the cause of cirrhosis: if possible to

Slow the progression of the disease.

Usually specific

POST-HEPATITIS CIRRHOSIS

Aetiology: Following infection with hepatitis viruses B, C & D.

Pathology:

1. Pathological features of cirrhosis.
2. May be pathological features of chronic active hepatitis.
3. In HBV: ground-glass appearing hepatocytes which are full of HBsAg (positive orcein).
4. In HCV: lymphocytes aggregates, fatty changes and bile ducts injury.

Clinical Picture:**1. Clinical picture of cirrhosis (See before).**

2. Positive past history of viral hepatitis may be present.

Investigations:**3. Investigation for cirrhosis (See before).**

1. Detection of hepatitis markers (see hepatitis).

Treatment:**4. Therapeutic measures for cirrhosis (as above).**

1. Prophylaxis against viral hepatitis.

CARDIAC CIRRHOSIS

Aetiology:

It is due to chronic severe congestion of the liver in cases of:

1. Chronic right ventricular failure.
2. Tricuspid valve disease (stenosis & incompetence).
3. Constrictive pericarditis and pericardial effusion.
4. High inferior vena cava obstruction.
5. Budd-Chiari syndrome.
6. Veno-occlusive disease.

Pathology:

1. Centrilobular congestion.
2. Pathological features of cirrhosis.

Clinical Picture:

1. Features of the cause e.g. right ventricular failure.
2. The liver is **enlarged**, firm and **tender** with sharp edge & smooth surface. Splenomegaly & ascites are common.
3. **Clinical picture of cirrhosis (See before).**

Budd-Chiari Syndrome

Aetiology: obstruction of the main hepatic veins :

1. Thrombosis (Hypercoagulability – thrombophilia):- defect in protein C&S - polycythaemia – contraceptive pills – Behcet's disease.
2. Malignant tumours e.g. hypernephroma.
3. Abdominal trauma.
4. Iatrogenic.

Clinical picture: Patients may present with 2 forms:

1. **Acute form:** presenting with acute abdominal pain, vomiting, tender hugely enlarged liver, ascites and mild jaundice.
Acute liver failure & portal hypertension may occur.
2. **Chronic form:** presenting with features of cardiac cirrhosis

N.B: *Caudate lobe is enlarged (hyperactive) as it has its own drainage to I.V.C. without hepatic veins*

Veno-occlusive Disease (VOD)

Aetiology: obstruction of intra-hepatic small and medium-sized veins:

1. Ingestion of pyrrolizidine alkaloids (e.g. in Senecio & Crotolaria plants).
2. Certain cytotoxic drugs.
3. Following BMT.

Clinical picture:-

It usually affects children & presents with Budd-Chiari-like syndrome.

BILIARY CIRRHOSIS

Aetiology: It is due to long standing biliary obstruction:

- Primary biliary cirrhosis (See jaundice).
- Secondary biliary cirrhosis :- causes of extra- hepatic obstructive jaundice (See jaundice)

Pathology:-

1. Dilatation & proliferation of bile ducts.
2. Pathological features of cirrhosis.

Clinical Picture:-

1. Features of obstructive jaundice (as above).
2. Features of the cause of obstructive jaundice.
3. The liver is enlarged, firm & with sharp edge.
4. ***Clinical picture of cirrhosis (See before).***

Investigations:-

1. Investigation for cirrhosis (See before)
2. Investigations for obstructive jaundice (See before)

Treatment:-

1. Relief of biliary obstruction.
2. Symptomatic treatment e.g. cholestyramine for pruritus.
3. Therapeutic measures for cirrhosis (See before).

**PRIMARY BILIARY CIRRHOSIS
(PBC)**

Def: Immunological progressive destruction of intra-hepatic bile ducts leading to cholestasis then cirrhosis and liver failure.

Pathology: Autoimmune disorder

- Infiltration of portal tracts by lymphocytes & plasma cells.
- Destruction of small bile ducts.
- Pathological features of cirrhosis appear in later stages of the disease.

Clinical picture:-

- Type of patient: females (90 % of cases) between 40-60 years.
- Early: Pruritus, fatigue and dry mouth and eyes are the initial symptoms in > 50 % of patients and may occur months or years before jaundice.
- Obstructive jaundice: (as above)
- Local examination: The liver is enlarged, firm & with sharp edge – Spleen is usually palpable.
- Association: Immune manifestations may be present e.g. Sjogren's syndrome.
 - Clubbing and skin pigmentation.

Clinical picture of cirrhosis (See before)

Investigations:**1. Investigations for obstructive jaundice e.g.**

- Alkaline phosphatase and γ -glutamyl transpeptidase (GGT):- elevated.
- Serum bilirubin:- normal in the early stages but elevation indicates disease progression and a worsening prognosis.

2. Detection of *antimitochondrial antibodies (AMA)*

- High IgM level
- Other autoantibodies (eg, ANA, anti-smooth muscle antibodies, Rh factor) may be present.

3. Liver biopsy:

- Shows characteristic histological Features divided into 4 stages

4. Investigations for cirrhosis (see before)

- **Stage 1** : Inflammation at portal areas
- **Stage 2**: Inflammation at portal and periportal areas
- **Stage 3**: Bridging fibrosis
- **Stage 4**: Cirrhosis

DD:

- Autoimmune cholangitis: as PBC with AMA absent.
- Primary sclerosing cholangitis: as PBC with extra-hepatic biliary affection.

Treatment:**1. Treatment of complications of cirrhosis (as above)****2. Supportive & symptomatic:-**

- Ursodeoxycholic acid (15 mg/kg/day) – side effect is diarrhea
- For pruritus: Cholestyramine (6-8 gm/day), ultraviolet light, rifampin or an opioid antagonist (naltrexone).
- Antifibrotic (colchicines- Penicillamine – cyclosporine) of doubtful value.
- Liver support by multivitamins and essential amino acids.

3. Hepatic transplantation: it is the only curative treatment.**Cholestyramine:**

1. Binds bile salts and thus may aggravate malabsorption.
2. Can decrease absorption of ursodeoxycholic acid..

HAEMOCHROMATOSIS**(Bronzed diabetes, Iron overload)**

Def: metabolic disorder characterized by iron overload resulting in pathological deposition of iron within parenchymatous organs and the skin.

Aetiology:**1. Hereditary haemochromatosis (Idiopathic):**

- Inherited disease caused by a defect in controlling iron absorption, leads to iron deposition in various organs (Liver iron > 100 times above normal).
- Gene on chromosome 6 (A.R.)
- The underlying defect is unknown but there is increase in the intestinal iron absorption.

2. Secondary haemochromatosis:

- Repeated blood transfusions.
- Chronic haemolytic anaemia especially thalassaemias.
- Repeated iron injections.
- Rarely excessive oral intake of iron.
- Sideroblastic anaemia.

Clinical Picture:-

Type of patient: males – between 40 – 60 years.

Menstruation and pregnancy probably account for the lower presentation in women

Organs affected:

- Liver: hepatomegaly, liver cirrhosis and may progress to Hepatocellular carcinoma (the commonest cause of death)
- Skin: bronzed pigmentation.
- Pancreas: Diabetes mellitus.
- Heart: Cardiomyopathy.
- Joint: Arthropathy.
- Genitalia: Testicular atrophy.
- Neurological: Pituitary failure.

Clinical picture of cirrhosis (See before)**Investigations:****1. Investigations for cirrhosis:** (see before)**2. Investigations for iron metabolism:-**

- Serum iron: increased (N: 70 – 170 μ g %).
- TIBC: decreased (N: 250 – 450 μ g %).
- Transferrin saturation: increased (N: 20 – 50 %)
- Serum ferritin: increased (N: 10 – 250 pg/L).

***Serum iron,
Saturation and
Ferritin increased***

3. Abdominal CT & MRI: can detect excess iron deposition in the liver.**4. Liver biopsy:**

- Increased liver iron concentration.
- Pathological features of cirrhosis.

Treatment:**1. Diet:-**

- Limiting intake of alcoholic, vitamin C (increases iron absorption) and red meat (high in iron).
- Inhibiting iron absorption by increasing intake of high-tannin tea, calcium and foods containing oxalic and phytic acids.

2. Repeated venesection (blood donation):- Initiated at ferritin > 300 mg/L (or 200 in nonpregnant women)- as 500 cc \ week ferritin drops at 20 mg/L – then 1-4 times \ year.

(Every bag of blood (500 ml) contains 200 -250 milligrams of iron).

3. Iron chelating agent desferrioxamine (desferal 0.5-1 gm/d).

4. Symptomatic treatment: e.g. Treatment of organ damage (heart failure with diuretics and ACE inhibitor therapy – treatment of diabetes).

5. Liver transplantation.

 α_1 - ANTITRYPSIN DEFICIENCY

α_1 - Antitrypsin is a neutrophil elastase inhibitor synthesized by hepatocytes and monocytes.

Pathophysiology and clinical picture:-

Liver: accumulation of α_1 -antitrypsin precursor molecules causes neonatal cholestatic jaundice (10 – 20%), cirrhosis in childhood (10%) or adult cirrhosis (10%) with increases the risk of liver cancer.

Lung: neutrophil elastase activity leads to tissue destruction leading to emphysema in Smokers before age of 45 (cigarette smoke increases protease activity)- Nonsmokers without occupational exposures at any age or family history of emphysema or unexplained cirrhosis.

Other organs:

Life-threatening hemorrhage – Aneurysms – Ulcerative colitis – ANCA – positive vasculitis – Glomerular disease.

Investigation:

X-ray chest: lower lung emphysema.

Serum α_1 -antitrypsin levels <80 mg/dL (< 11 μ mol/L)

Treatment of pulmonary disease:

Purified human α_1 -antitrypsin (60 mg/kg IV over 45 to 60 min given once weekly) – not improve damaged lung structure but stop progression.

WILSON'S DISEASES**(Hepato-Lenticular degeneration)**

Def: an autosomal recessive genetic disorder in which copper accumulates in tissues: this manifests as neurological and liver disease

Aetiology:

Autosomal recessive disorder characterized by excess deposition of copper in various organs.

The underlying defect is unknown but there is decrease in hepatic excretion of copper and decrease in serum ceruloplasmin (see copper metabolism).

Clinical Picture:

Liver: liver cirrhosis (the commonest form), chronic active hepatitis or acute hepatitis.

Basal ganglion: Extrapyrimalidal syndromes as parkinsonism and chorea.

Eye: Kayser-Fleischer ring: greenish brown ring in the cornea
(Slit-lamp examination is a must)

Kidney: Renal tubular dysfunction as Fanconi syndrome or RTA (renal tubular acidosis).

Blood: Haemolytic anaemia.

Investigations:**Investigations of copper metabolism:-**

Serum ceruloplasmin and copper levels: Decreased.

Urinary copper: Increased.

Liver investigations:-

Liver biopsy: Increased liver copper concentration.

Investigations for cirrhosis (See before)

Neurological investigations:-

Magnetic resonance imaging (MRI):- shows hyper-intensities in the basal ganglia

Treatment:-

1. Copper chelating agent as penicillamine.
2. Maintenance therapy by zinc may be used (Prevents copper absorption)
3. Symptomatic treatment e.g. for parkinsonism.
4. Liver transplantation.

Copper metabolism: Copper acts as a cofactor for a number of enzymes

Action of liver:-

1. Copper carried by ceruloplasmin and released into the bloodstream.
2. Removing excess copper by secreting it into bile.

In wilson's disease

- Liver: Decreased copper excretion in the bile = accumulation in the liver tissue = decreased ceruloplasmin = releasing of free copper (non-ceruloplasmin bound) into the bloodstream.
- Brain: deposited in the basal ganglia called the lenticular nucleus (putamen and globus pallidus)
- Haemolysis: direct effect of free copper.

ALCOHOLIC CIRRHOSIS

Aetiology: Chronic excess consumption of alcohol

Toxic effect: Acetaldehyde converted to acetate (which is hepatotoxic)

Metabolic effect:

- Excess H ion which converts NAD to NADH.
- Lowers fatty acid oxidation and allows triglycerides to accumulate, causing fatty liver and hyperlipidemia.
- Also causing acidosis, hyperuricemia and may be gout.

Pathology:-

Alcoholic liver diseases (3)

- **Fatty liver** (steatosis) is the initial event and potentially reversible.
- **Alcoholic hepatitis** (steatohepatitis) is a combination of fatty liver, diffuse liver inflammation and liver necrosis.
- The damaged hepatocytes either are swollen (ballooning) or contain eosinophilic deposits in the cytoplasm (Mallory or alcoholic hyaline bodies).
- **Cirrhosis** is advanced cases
- Characterized by extensive fibrosis and micronodular cirrhosis.

Clinical Picture:-

1. History of prolonged alcohol intake
2. Clinical picture of cirrhosis (See before)
3. Associated features of chronic alcoholism may be present.
4. Parotid enlargement & Dupuytren's contracture may be present.

Investigations: *Investigations for cirrhosis (See before).*

+

Specific findings:-

- AST exceeds ALT by a ratio of > 2.

- GGT increases (ethanol-induced enzyme induction) a helpful to determine whether the patient is still taking alcohol or not.

CBC:

- Macrocytic anaemia
- Thrombocytopenia: BM suppression or hypersplenism.

Treatment:

1. Stoppage of alcohol intake.
2. Therapeutic acasures for cirrhosis (See before)
3. Treatment of nutritiomal deficiencies if present e.g. vitamin supplementation.

DD:

Non-alcoholic steatohepatitis (NASH)

Similar to alcoholic liver but patient does not have an alcohol history.

Biopsy is needed for diagnosis.

This type of hepatitis appears to be associated with diabetes, protein malnutrition, obesity, coronary artery disease, and treatment with corticosteroid medications.

Hazards of chronic alcohol Abuse

Neurological	-Wemicke-Korsakoff syndrome -Peripheral neuropathy. - Myopathy
Cardiac	-Cardiomyopathy
Liver	-Acute Fatty liver -Alcoholic cirrhosis -Chronic hepatitis - Zeive's syndrome -Hepatocellular carcinoma
GIT	-Acute & chronic gastritis -Acute & chronic pancreatitis - Malabsorption
Metabolic	-Hyperlipidaemia - Hyperuricaemia -Hypoglycaemia - Ketoacidosis
Haematological	-Macrocytic anaemia (hypovitaminosis) -Thrombocytopenia – Leucopenia (BM suppression or hypersplenism)

Evaluation of patient with chronic liver diseases***Child-Pugh Classification of Severity of Liver Disease:***

	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (gm/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time			
• Seconds over control	1-3	4-6	>6
• INR	<1.8	1.8-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Grade A: score 5-6 (well-compensated disease)

Grade B: score 7-9 (significant functional compromise)

Grade C: score 10-15 (decompensated disease)

These grades correlate with one-and two-year patient survival.

Grade	Score	One-year survival (%)	Two-year survival (%)
A	5-6	100	85
B	7-9	80	60
C	10-15	45	35

Laboratory studies Used in Diagnosing Chronic Liver Disease:-

	Laboratory tests and results
Alcoholic liver	- AST:ALT ratio >2 – Elevated GGT
a₁ –Antitrypsin deficiency	- Decreased serum a ₁ -antitrypsin - Genetic screening
Autoimmune hepatitis	- Positive ANA and/or ASMA in high titer
Chronic hepatitis B	- Positive HbsAg ± HbeAg - Hepatitis B virus DNA by PCR - ± Elevated AST and/or ALT
Chronic hepatitis C	- Positive hepatitis C virus antibody - HCV-RNA by PCR - ± Elevated AST and/or ALT
Hepatocellular carcinoma	- Elevated alpha fetoprotein, AST ± ALT - Elevated ALP with obstruction or cholestasis
Haemochromatosis	- Fe profile – liver biopsy - Haemochromatosis gene study
NASH	- Elevated AST ± ALT - Ultrasound and/or biopsy are necessary
PBC and PSC	- Cholangiography - Positive antimitochondrial antibody (PBC) or antineutrophil cytoplasmic antibody (PSC) - Elevated AST, ALT, and ALP common.
Wilson's	- Reduced serum ceruloplasmin-low serum copper level - Increased urinary copper excretion

LIVER FAILURE

Def:- is the inability of the liver to perform its normal synthetic and metabolic function as part of normal physiology.

Two forms: Acute liver failure and chronic liver failure.

Aetiology:

As causes of Hepatocellular jaundice

1. Infections:

- Viral hepatitis (CMV, herpes, EB-V and yellow fever).
- Septicaemia and multiple multiple pyaemic abscesses.
- Leptospirosis and toxoplasmosis.

Drugs & toxins:

- Alcohol, halothane, isoniazid & paracetamol.
- Carbon tetrachloride & D.D.T. – Atebrine – Phosphorus.

3. Acute fatty liver of pregnancy

4. Reye's syndrome

5. Budd-Chiari syndrome

6. Liver cirrhosis

7. Chronic active hepatitis

8. Terminal cases of obstructive jaundice

9. Malignancy : e.g. metastases

10. Lucey-Driscoll syndrome:- Inhibition of UGT by a substance in the maternal serum.

11. Breast milk jaundice: inhibition of UGT by a substance in the breast milk (free fatty acids or B-glucuronidase).

12. Hereditary diseases (as above)

Clinical Manifestations

1) Failure of Health (fatigue):- Anorexia, loss of weight, easy fatigability & weakness.

Explanation: marked disturbance of metabolism, bacteraemia and endocrinal abnormalities

2) Fever: it is a low-grade fever (<38.3).

Explanation:

- **Bacteraemia:** bacteria from the intestine pass through the diseased liver without elimination or bypass the liver through porto-systemic shunts to reach the general circulation.

((F))

1. Failure of health (fatigue)
2. Fever
3. Feto Hepaticus
4. Flapping tremors
5. Ascites
6. Encephalopathy
7. Jaundice
8. Skin (cutaneous)
9. Endocrinal
10. Blood
11. C.V.S
12. Kidney

- Damage of liver cells leading to release of **pyrogens**

3) **Fetor Hepaticus**: It is a sweetish, musty, faecal odour of breath.

Explanation:-

- Production of mercaptans by the action of bacteria on intestinal proteins.
- These mercaptans pass through the diseased liver without detoxification or bypass the liver through porto-systemic shunts & appear in breath.

4) **Flapping tremors**

5) **Ascites & oedema**:

- Clinical picture of ascites (See later).
- Oedema usually follows the ascites +/- pleural and pericardial effusions.
- Ascites may develop chronically as a result of gradual deterioration in liver function or acutely e.g. after GI haemorrhage or sepsis.

Explanation: (Pathogenesis)

1. **Hypoalbuminaemia**: due to diminished hepatic synthesis of albumin leading to decreased plasma oncotic pressure.
2. **Salt & water retention**: due to
 - Secondary hyperaldosteronism.
 - Increased ADH.
 - Increased oestrogen
 - Diminished glomerular filtration
3. **Portal hypertension**:
 - Portal hypertension alone rarely produces ascites.
 - It mainly localizing factor of the transudate fluid into peritoneal cavity.
4. **Increased hepatic lymph production (Lymphorrhoea)**:
 - In cirrhosis & hepatic venous obstruction, there is increase in intra-sinusoidal pressure which increases hepatic lymph production.
 - When the rate of formation of lymph exceeds the rate of removal, the fluid extravasates into the peritoneal cavity.
5. **Increased incidence of (local factors)**: spontaneous bacterial peritonitis, tuberculous peritonitis & malignant ascites.

6) **Hepatic Encephalopathy**: (See later)

7) **Jaundice**: (See later)

8) Skin Manifestations (Coetaneous):**1. Palmar eruthema :** (liver palms)

It is an erythema in thenar, hypothenar eminences, opposite the distal heads of metacarpal bones and pulps of fingers with central pallor.

2. Spider naevi:

- Dilated central arteriole with radiating capillaries, pressure on the central arteriole causes blanching of the radiating capillaries.
- Spider naevi are found in the distribution of SVC
- May be in mucous membranes of nose & mouth and can bleed.

3. Paper-money skin:

Randomly scattered small vessels through the skin & have the same distribution of spiders.

Explanation:- excessive vasodilators (vasodilator materials = (VDMs)

1-Oestrogen

2-Vasoactive intestinal peptides (VIP)

3-Substance B

4- Nitric oxide

5- GABA

6-Endothelial factors, prostaglandins.

4. White nails: Opacity of the nail bed due to hypoproteinaemia.

N.B. parotid enlargement may also occur due to hypoproteinaemia.

9) Endocrinal manifestations:**A- Androgenic and gynecological:**

In males: (Feminization)	In females: (De-feminization)
1. Gynaecomastia	1. Atrophy of breasts
2. Feminine distribution of suprapubic hair & decreased body hair	
3. Decreased libido, impotence, testicular atrophy & sterility.	2. Decreased libido, amenorrhoea & infertility

Explanation:

- Increased oestrogen
- Decreased testosterone
- Decreased activation of testosterone in the liver to dihydrotestosterone.
- Increased sex hormone-binding globulin (SHBG) (the most accepted)

B- Defect metabolism of some hormones:- eg, hyperaldosteronism – increased ADH (sharing in mechanism of ascites and oedema)

10) Blood manifestations (hematological):**A. Bleeding tendency:** due to

1. Deficiency of coagulation factors especially:
 - Hypoprothrombinaemia & hypofibrinoginaemia
 - Diminished factors V, VII, IX, X.
2. Thrombocytopenia: due to hypersplenism.
3. Platelet dysfunction.

B. Anaemia: may be

1. Hypochromic microcytic anaemia: due to repeated haemorrhages e.g. from oesophageal varices.
2. Normochromic normocytic anaemia: due to hypersplenism & B.M. depression.
3. Macrocytic anaemia: due to deficiency of folic acid & vitamin B 12 (rare).

C. Pancytopenia: may occur due to hypersplenism or B.M. depression.**11) Cardiovascular manifestations:****1. Hyperkinetic circulation:**

- Probably due to increased vasodilator materials.
- The diseased liver may produce or fail to metabolize such vasodilator materials.

2. Central cyanosis & clubbing: due to

- Pulmonary arterio-venous shunts due to vasodilator materials (hepato-pulmonary syndrome)
- Porto-pulmonary shunts.
- Basal lung collapse due to tense ascites.

12) Hepato-Renal syndrome (Kidney):

Def: functional but not structural renal impairment in patients with advanced liver failure.

Precipitated by vigorous diuretics, paracentesis, diarrhea or sepsis

Explanation: Abnormalities in the splanchnic vascular tone

Activation of renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system and **vasoconstriction of the kidneys** (decreased glomerular blood flow & GFR)

Type I	Type II
Rapidly progressive (< 2 weeks)	Slowly progressive
Very poor prognosis (> 50% survival)	

13) Increased incidence of infections:

e.g. spontaneous bacterial peritonitis & bacteraemia

14) Impairment of carbohydrate metabolism:

- In acute liver failure: may be hypoglycaemia.
- In chronic liver failure: may be impaired glucose tolerance & rarely diabetes mellitus.

15) Features of the cause:

e.g. features of portal hypertension (as bleeding oesophageal varices) in patients with cirrhosis.

Investigations

1. Liver function tests:

- **Plasma proteins:** decreased albumin, increased globulins and A/G ratio is decreased & may be reversed.
- **Prothrombin time:** prolonged & not corrected by IV vit. K.
- **Serum bilirubin:** increased biphasic
- **Enzymes:** transaminases & alkaline phosphatase are usually elevated (Dropped enzymes indicate terminal case)
- **Blood ammonia:** elevated (not in all cases and of little value)

2. Liver imaging: e.g. abdominal ultrasound, CT scan & isotopic scanning) may be helpful for detection of the underlying cause e.g. cirrhosis.

3. Investigations for the cause: e.g. hepatitis markers.

4. Investigations for precipitating factors: e.g. serum K.

Treatment

I. Treatment of the cause: if possible

e.g. stoppage of hepatotoxic agents (to avoid further progression)

II. Treatment of precipitating factors: if present

e.g. infections, hypokalaemia.

III. Treatment of hepatic encephalopathy: (see later)

IV. Symptomatic treatment: e.g.

- ***Treatment of hepatic encephalopathy*** (see above)
- ***Treatment of ascites*** (see later)
- ***Treatment of bleeding tendency:*** Fresh frozen plasma to replace the deficient coagulation factors.

V. Hepatic Transplantation: (see later)

It is the only curative treatment of liver failure.

HEPATIC ENCEPHALOPATHY

Def: it is a neuropsychiatric syndrome that may complicate severe liver disease and or extensive porto-systemic shunting.

Pathogenesis: remains unclear & possible mechanisms include:

A. Production of toxic substances:

- ✓ by the action of bacteria on intestinal proteins.
- ✓ These toxins pass or the diseased liver without detoxification to systemic circulation
- ✓ can cross the blood brain barrier cause disturbance of cerebral metabolism resulting in encephalopathy.

The possible toxic substances include:

1. Ammonia: possibly acting through interference with Krebs's cycle leading to diminished production of energy required by brain cells.
2. Other gut-derived toxins: Benzodiazepine like substances, gamma-aminobutyric acid (GABA), short-and medium-chain neurotoxic fatty acids, phenols and mercaptans.

GABA, the principal inhibitory neurotransmitter in the brain, is also produced in the gut with decreased hepatic clearance, this substance enters brain and inhibits neurotransmission.

B. Disturbance of amino acids: Increased aromatic amino acids & decreased branched-chain amino acids leading to decreased production of normal neurotransmitters (as noradrenaline) and formation of false neurotransmitters (as octopamine).

Increased inhibitory neurotransmitters	Decreased excitatory neurotransmitters
▪ Benzodiazepines ▪ GABA ▪ Serotonin	▪ Glutamate ▪ Dopamine ▪ Aspartate ▪ Catecholamines

C. Benzodiazepine hypothesis:

There is a GABA/ benzodiazepine/ barbiturate receptor complex, so GABA, stimulate other receptors producing exaggerated inhibitory action

D. Increased permeability of blood-brain barrier: which facilitates the passage of toxins into the brain cells

E. Alkalosis & hypokalaemia: increase renal production of ammonia & increase its passage through the blood-brain barrier.

F. Other contributing factors:

- CSF glutamine levels correlate closely with degree of HE.
- Decreased cerebral blood flow and oxygen
- Increased glucose consumption and possible hypoglycemia
- Zinc deficiency
- Manganese may deposit in basal ganglia and induce extra-pyramidal symptoms.

G. Porto-systemic encephalopathy:- can develop spontaneously as the liver disease progresses and shunting increases, more commonly, drugs or other complications of cirrhosis can unmask it.

Precipitating Factors:

<u>Increased nitrogen load</u>	- Gastrointestinal bleeding (decrease hepatic blood flow) - Excess dietary protein - Azotemia - Constipation - Transfusion of stored blood rich in ammonia
<u>Electrolyte imbalance</u>	- Hyponatremia (after severe diarrhea or vomiting) - Hypokalemia - Metabolic alkalosis/acidosis - Hypoxia - Hypovolemia
<u>Drugs</u>	- Narcotics, tranquilizers, sedatives
<u>miscellaneous</u>	- Infection - Surgery - Superimposed acute liver disease - Progressive liver disease - Transjugular intrahepatic portal-systemic shunt (TIPS)

Clinical Picture: (Pass through 2 stages)**1. Pre-Coma: (2S – 3A – 2D)**

- Sleep disturbances: hypersomnia & inverted sleep rhythm.
- Speech disturbances: slow slurred speech or monotonous speech
- Apathy
- Asterixis (flapping tremors):- rapid flexion & extension movements at the wrist & metacarpo-phalangeal joints seen in the extended hands.
- Apraxia e.g. inability to reproduce simple design with matches.
- Disturbed personality & behavior: e.g. childishness, irritability & loss of concern for family.
- Disorientation for time, place & persons.

2. **Coma:** Irritable coma, rigidity, hyprrflexia, rarely convulsions & finally death.

Stages hepatic encephalopathy:

- Stage I: Apathy, restlessness, inverted sleep rhythm.
- Stage II: Drowsiness, disorientation, asterixis.
- Stage III: Stupor
- Stage IV : Coma

Bedside test for early detection of early hepatic encephalopathy:

- Eg., cross-matching test
- Number connection test

Investigation (as above) +

Neuro-physiological study:

- EEG
- Visual evoked responses

Treatment of hepatic encephalopathy:-

1. General

- A. Hospitalization & rest in bed
- B. Care for the comatose needed in patients with coma.

2. Nutritional management

A. Protein:-

- Restricted to 0.5-1 gm/kg/day to avoid rise in ammonia & other nitrogenous toxins.
- In severe cases, all proteins are eliminated.
- Vegetable proteins are preferred

B. Carbohydrates: given in excess to insure adequate caloric intake and limit protein catabolism

C. Electrolytes: excessive potassium supplementation as fruit Juices

D. Lipid: better avoided as usually nauseating

3. Gut affecting (Reduction of Nitrogenous load arising from the Gut)

A. Bowel cleansing (Colonic lavage)

To reduce the luminal content of ammonia, decrease colonic bacterial counts and lower blood ammonia. Lactulose enemas may be used.

B. Non-absorbable disaccharide: (first-line pharmacological treatment)

Lactulose: (15-30 ml 8-hourly)

It is a synthetic disaccharide splitted by intestinal bacteria into:

1. Lactic acids (bactero-static) reduce fecal pH to be unsuitable to bacterial flora.
2. Lactose (Osmotic Laxative)
Side effects: diarrhea, flatulence
Lactitol is a more palatable than lactulose with fewer side effects.

1. General
2. Nutritional
3. Gut
4. neurological
5. interventional

C. Antibiotics:

- **Neomycin** (1-4 g /4-6-hourly) reducing the bacterial content of the bowel.
- It can be used in addition or as an alternative to lactulose
- Neomycin is poorly absorbed from the bowel
- Long-term use may lead to ototoxicity and or nephrotoxicity
- **Metronidazole** may be used

D. Others:- Ornithine aspartate drug provides substrates for the urea cycle (ornithine) as well as for the synthesis of glutamine (aspartate via transamination to glutamate)

4. Neurologically acting drugs (Altering Neurotransmission)**A. Sedatives:**

Are better avoided but if necessary small doses of oxazepam or diazepam are given. Morphine is contraindicated.

B. L-dopa & Bromocriptine:

May be used to improve neurotransmission

C. Flumazenil: benzodiazepine receptor antagonist**5. Interventional:**

A. Artificial hepatic support: e.g. using charcoal haemoperfusion

B. Hepatic Transplantation:

It is the only curative treatment of liver failure.

FULMINANT (ACUTE) HEPATIC FAILURE

Definition: Clinical syndrome developing as a result of massive necrosis of liver cells or following any other cause of sudden and severe impairment of hepatic function, **occurring in patients without pre-existing liver disease.**

Types:-

Hyperacute	- Encephalopathy within 7 days (1 week) of onset of jaundice very high risk of cerebral oedema.
Acute	- Encephalopathy within 1-4 weeks - High risk of cerebral oedema
Subacute	- Encephalopathy within 5-26 weeks - Low risk of cerebral oedema

The key features of hepatic failure are hepatic encephalopathy, severe coagulopathy and jaundice (triad)

Aetiology: (as acute causes of hepatic failure)

- 1. Infections:**
- 2. Drugs & toxins:**
- 3. Acute fatty liver of pregnancy**
- 4. Reye's syndrome**
- 5. Budd-Chiari syndrome.**

Clinical Picture:

Manifestations of hepatic encephalopathy are often the first & most important:

- Early: disturbed personality & behavior
- Restless, delirium & mania
- Asterixis & convulsions
- In the later stages: come with decerebrate rigidity
- The condition may be misdiagnosed as encephalitis or acute psychosis.
- Feter hepaticus.
- Jaundice is mild in early stages & becomes deep later
- Liver size is usually small
- The condition is usually fatal due to encephalopathy, haemorrhage, respiratory failure, circulatory failure, renal failure, cerebral oedema, infection, hypoglycaemia or DIC.

Investigations:**1. Liver function tests:**

- Prothrombin time is prolonged & serum albumin is initially normal but later becomes low.
- Serum bilirubin is elevated & may be used to assess prognosis.
- SGPT & SGOT are elevated early & may remain high or fall later due to extensive loss of liver cells.
- Blood ammonia is elevated but of little value.

2. Liver imaging: e.g. abdominal ultrasonography usually show reduced size of liver.

3. Investigations for the cause: e.g. viral markers.

4. EEG: occur early & the test is useful for diagnosis & to assess prognosis.

Treatment:

- 1. Hospitalization:** and care of the comatose patient.
- 2. Treatment of the cause:** If possible (e.g. stoppage of hepatotoxic agents) to avoid further progression of the condition.

3. **Treatment of precipitating factors:** e.g. infections, hypokalaemia.
4. **Treatment of hepatic encephalopathy** (as before)
5. **Correction of complications:** e.g. cerebral oedema, hypoglycaemia, infection, renal, respiratory or circulatory failure.
6. **Artificial hepatic support:** e.g. using charcoal haemoperfusion.
7. **Hepatic transplantatio**

PORTAL HYPERTENSION

Definitions: Pathological increase in the portal venous pressure and formation of portosystemic collaterals.

Portal vein carries about 1500 ml/min of blood with pressure about 5-10 mm Hg. Portal hypertension diagnosed as portal pressures over 12mm Hg.

Causes**A. Pre-hepatic :** (portal vein lesions)

- | | |
|--------------------------------------|----------------------------|
| 1. Portal vein thrombosis | 4. Splenic vein thrombosis |
| 2. Splanchnic arterio-venous fistula | 5. Dehydration |
| 3. Polycythaemia | 6. Tumours |

B. Intra-hepatic

(a) Pre-sinusoidal	(b) Sinusoidal +/- post sinusoidal
1. Schistosomiasis 2. Idiopathic portal hypertension 3. Myeloproliferative diseases 4. Polycystic diseases 5. Hepatic metastasis:-leukemia 6. Granulomatous lesions:-TB, sarcoidosis	1. Hepatic cirrhosis 2. Peliosis hepatitis (AIDS) 3. Veno-occlusive disease 4. Acute alcoholic hepatitis

C. Post-hepatic (causes of cardiac cirrhosis)

- | | |
|------------------------------|-----------------------------------|
| 1. Budd-chiari | 2. Inferior vena cava obstruction |
| 3. Right sided heart failure | 4. Constrictive pericarditis |
| 5. Tricuspid lesions | |

Clinical picture

History of: Contact to water canal

Drugs: alcohol intake – hepatotoxic agent – contraceptive

Operative: blood transfusion – abdominal sepsis – neonatal umbilical sepsis

Diseases: myeloproliferative disorders (leukemia)

Present history

- Haematemesis with or without melena
- Dyspepsia and epigastric pain :- gastric congestion
- Constipation and distension :-intestinal congestion or ascites
- Left sided pain :- huge spleen

Physical examination

A. General:

- Pallor (hypersplenism – cirrhosis)
- Evidence of hyperdynamic state may be seen
- General feature of LCF (late cirrhosis)
- Muscle wasting (endemic diseases)

B. Local examination:

1. Splenomegaly: due to congestion and/or RES activity.

- The single most important diagnostic sign of portal hypertension
- Larger in young people and in macro-nodular rather than micronodular cirrhosis.
- May lead to hypersplenism.

2. Liver:

A. Size:

- Shrunk liver:- with intrahepatic causes (B-cirrhosis)
- Unchanged :- with prehepatic causes (portal or splenic veins thrombosis)
- Enlarged and may be tender:- with suprahepatic causes and Pulsating liver is seen in tricuspid valve lesions.

B. Liver consistency:

- A soft liver: extra-hepatic portal venous obstruction.
- Firm: supports cirrhosis.

3. Ascites:

- Early ascites: acute portal or splenic vein thrombosis.
- Late: related to additional factors as hypoalbuminaemia.

4. Porto-systemic anastomosis:

	Location	Portal circulation	Systemic circulation	Clinical consequence
I	Proximal stomach and distal esophagus	Coronary vein of stomach	Azygos vein	Gastroesophageal varices.
	Anorectal	Superior hemorrhoidal	Middle and inferior hemorrhoidal	May be mistaken for hemorrhoids
II	Anterior abdominal wall	Peraumbilical vein (left portal)	Superior & inferior epigastric veins	Caput medusa

III	Retroperitoneal	Visceral veins	Left renal vein Abd. Wall vein Retroperitoneal y.	1. Liver & diaph 2. Spleen & diaph 3. Intestine & post Abd. wall.
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Major sequelae of portal hypertension:-

- 1. Oesophageal varices:**
- 2. Other sites of varices:** e.g. gastric, duodenal, colonic and anorectal varices.
- 3. Splenomegaly:** CBC shows pancytopenia (hypersplenism)
- 4. Ascites:** explained by portal hypertension and hypoalbuminaemia
- 5. Hepatic encephalopathy:** mainly the chronic form.

Investigations

I. Laboratory:

No specific test is suggestive of portal hypertension, however, abnormal **liver functions test** may give an idea about the cause.

CBC: evidence of hypersplenism.

Occult blood in stools: portal hypertension with minor GIT bleeding

II. Visualization of the portal system:

Dilatation of the portal vein and the presence of shunts will indicate portal hypertension. Several methods may be used:

- 1. Ultrasound / CTscan**
- 2. Digital subtraction angiography:** Injection of intravascular contrast media with subtraction of image taken before the injection.
- 3. Percutaneous trans-splenic venography:** A radio-opaque material is injected via the spleen into the portal circulation.
- 4. Umbilical vein catheterization**
- 5. Trans-hepatic venography**
- 6. Operative angiography:** Injection of contrast into the portal vein during operation.

III. Estimation of portal Pressure:

1. Percutaneous Intrasplenic Pressure:

- Needle introduced into the red bulb or the spleen.
- It is increased in pre and post sinusoidal causes (cirrhosis & B)

2. Wedged Hepatic Vein Pressure:

By catheterization rout up to the hepatic veins and pressure at site of catheter arrested (Wedged)

- This method measures the sinusoidal pressure.
- It is increased in post-sinusoidal and decreased in pre-sinusoidal causes.

3. Other methods:

1. Umbilical vein catheterization.
2. Trans-hepatic approach.
3. Operative techniques.

+ **Investigations of esophageal varices (see later)**

Esophageal varices

Dilated veins located at the lower part of the esophagus.

incidence	▪ Varices develop annually in 5% - 15% of patients with cirrhosis ▪ The varices enlarge by 5% - 10% each year ▪ Only 30% of them experience variceal bleeding ▪ Each episode of bleeding carries a 20% - 30% risk of death ▪ Up to 70% of patients who do not receive treatment die within 1 year
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Clinical picture:

1. Ruptured varices cause haematemesis, melaena or both
2. Repeated mild bleeding cause anemia
3. May precipitate hepatic encephalopathy

Risk factors for variceal bleeding:

Portal pressure >12 mm Hg

Varix size and location :- Large esophageal varices – Isolated cluster of fundal varices

Red signs in endoscopic examination:-Red wale – Cherry red spots – Diffuse erythema

Degree of liver failure:- child –pugh class C

Presence of ascites :- Tense ascites

Investigations:

As in portal hypertension +

1. Detection of the Varices: Either by endoscopy or barium swallow.

Oesophageal or gastric varices indicate the presence of portal hypertension.

Value of Endoscopy:-

- Detects early varices
- Grades the varices
- Detects signs of impending rupture
- Can be used for sclerotherapy of varices.
- Detects gastric varices

Treatment of portal hypertension and varices

Summarized as**I- Bleeding Varices:**

- A. General Measures
- B. Pharmacological control
- C. Interventional therapy:- Endoscopic therapy-TIPS-others
- D. Emergency Surgery

II. Non-bleeding Varices:**A) Primary prophylaxis Drugs****B) Secondary prophylaxis**

- A. Sclerotherapy
- B. Surgical
- C. Drugs as primary prophylaxis

1. Management of Bleeding Varices:**A. General Measures (Haemodynamic resuscitation)**

- **Hospitalization**
- **Blood transfusion:** this must be fresh to contain coagulation factors & to have minimal amount of ammonia.
- Vitamin K and or platelet transfusion
- Sedatives are better avoided
- Endoscopy: To define the site of haemorrhage (better to be for diagnosis and therapeutic measures at the same session)

B. Pharmacological control**1. Vasopressin (Pitressin)**

Action: Vasoconstriction of visceral arterioles will lead to diminished portal pressure and controlling about 60% - 75% of variceal bleeding episodes.

Administration: 20 U in 100 ml glucose 5% I.V. slowly.

Side effects: Blanching, colic, vomiting & diarrhea.

Contraindications:

- Ischaemic heart: induce coronaries vasoconstriction.
- Pregnancy: induce contraction of the uterus.
- Uncontrolled hypertension: As it increases peripheral resistance.

2. Glypressin:

Action: Synthetic derivative of vasopressin, but it controls variceal bleeding better than vasopressin.

Administration: 2 mg/6 hours intravenously, maximally for 24 hours

3. Synthetic Somatostatin (Sandostatin)

This is a synthetic growth hormone release inhibiting factor (GH-RIF). It gives the same effect of glypressin but with less side effects.

4. Octreotide: (Sandostatin)

Action: Synthetic, long-acting analogue of somatostatin. Inhibits the release of vasodilatory hormones (eg, glucagon), it indirectly causes splanchnic vasoconstriction and decreased portal flow.

Administration: Loading dose about 50 micrograms, followed by an infusion of 50 ug/hr, up to 5 days.

C. Interventional therapy**1. Endoscopic therapy: (injection-band ligation)**

Remains the first-line therapy for active variceal bleeding

A. Injection Sclerotherapy:

A sclerosant (ethanol amine oleate) is injected into a varix under direct vision during endoscopy.

This causes tissue edema and mechanical compression followed by inflammation, variceal thrombosis, fibrosis and, finally, obliteration.

Complications:

- | | |
|----------------------|---|
| 1. Bleeding ulcers | 2. Dysphagia due to stricture formation |
| 3. Pleural effusions | 4. Aspiration pneumonia |
| 5. Bowel perforation | 6. Acute respiratory distress syndrome |

B. Band ligation:

Elastic bands are placed around varices using a device attached to the endoscope, leading to ischemic necrosis, thrombosis, fibrosis and falling.

Less complicated and less operator dependent.

C. Injection of tissue Adhesives (Glue):

Used for injection of gastric varices & big oesophageal varices.

The used material is called "Histoacryl blue"

2. Transjugular intrahepatic portosystemic shunt (TIPS)

An angiographically created shunt between hepatic and portal veins that is kept open by placement of a fenestrated metal stent

Primarily used when pharmacologic and endoscopic treatment of acute bleeding is unsuccessful.

Immediate complications:

Secondary bleeding
Worsening encephalopathy

Long-term complications

Stent stenosis or occlusion
Porto-systemic encephalopathy

Trans-Hepatic Variceal Sclerosis: A catheter is introduced trans-hepatic into the portal vein and the left & short gastric veins are selectively catheterized & injected. (**highly invasive**)

3. Sungstaken-Blackmore Tube: 3 lumen tube

- For gastric aspiration or feeding.
- For inflating gastric balloon (100 ml water)
- For inflating oesophageal balloon (40 mml air)
- Fourth tube for aspiration of secretion so called 4 lumen tubes

Indication: if endoscopy is not available, contraindicated or absence of expert hands.

Percussions: For less than 48 hours.

Complications: 1/esophageal ulceration.
2/Pneumonia, lung abscess & asphyxia

D. Emergency Surgery:

- Ligation of bleeding varices.
- Oesophageal transaction using the staple gun.
- Portal-caval shunt

E. Measures to Prevent Encephalopathy: as above.**II. Management of Non-bleeding Varices****A) Primary prophylaxis (for prevention of initial bleeding episode)**

All patien with cirrhosis should undergo endoscopy to screen for varices every 2 to 3 years.

Drugs:

Beta blockers: Both propranolol hydrochloride (Inderal) and nadolol reduce portal pressure through beta2 blockade.

The dose is adjusted to decrease the resting heart rate by 25%

Nitrates may be used.

B) Secondary prophylaxis (for prevention of recurrent bleeding)**1. Interventional:- for complete eradication of varices.**

Sclerotherapy: Injection is repeated monthly till varices disappear, then follow up & re-injection at wider intervals.

Band ligation of oesophageal varices

Tissue adhesives: for gastric varices.

2. Surgical:

Tunner's & modified Tunner's operation

Shunt Operations:

- Porta-caval shunt.
- Distal spleno-renal shunt. (Warren's operation)

3. Medications as primary prophylaxis: B-blokers.

Gastrointestinal bleeding

HAEMATEMESIS: Vomiting of blood.

Causes:

Esophageal Causes:

1. Rupture esophageal varices
2. Esophagitis & peptic ulceration of esophagus.
3. Carcinoma of the esophagus.
4. Rupture of aortic aneurysm into the esophagus.
5. Mallory-Weiss syndrome: Laceration of esophago-gastric junction due to severe vomiting.

Gastro-Duodenal Causes:

1. Acute gastritis or acute gastric erosions (ulcers) especially due to salicylates, phenyl-butazone & cortisone.
2. Chronic peptic ulcer whether gastric or duodenal.
3. Hiatus hernia
4. Cancer stomach & rarely cancer ampulla of Vater.
5. Peutz-Jeghers syndrome: G.I. polyposis & mucocutaneous pigmentation.

General Causes:

1. Haemorrhagic blood diseases :- haemophilia \ purpura
2. Haemorrhagic fevers:- plague & relapsing fever.
3. Severe hypertension.

False Haematemesis:

Ingestion of blood after bleeding from the nose, mouth pharynx and vomiting of this blood

Differential Diagnosis:

- 1-Differentiation from haemoptysis (see chest)
- 2-Differentiation from false haematemesis by local examination.
- 3-Differentiation of the cause through:
 - ♦ Good history
 - ♦ Physical examination
 - ♦ Endoscopy (the main diagnostic tool)
 - ♦ Barium swallow & meal
 - ♦ Liver functions, portal manometry & portal venography.
 - ♦ Gastric function tests.

MELAENA:

Def: Passage of tarry stools (usually offensive and bulky) due to presence of digested blood.

Mechanism:

- 1-Bleeding point above ileocecal valve (below this point = haematochezia)
- 2-More than 60 cc blood (less amount = occult blood)
- 3-Retained for more than 6 hours (rapid bowel = fresh blood)

Causes: (as above + intestinal causes)

- I- Oesophageal
- II- Gastro-duodenal
- III- Intestinal Causes:
 - Bleeding typhoid ulcer
 - Regional ileitis & tuberculous enteritis.
 - Cancer head of pancreas
- IV- General causes
- V- False melaena, due to ingestion of blood.

Differential Diagnosis:

- 1/Differentiation from (dark stools)
 - Ingestion of iron
 - Bismuth therapy
 - Haemolytic anemia
- 2/Differential diagnosis of the cause

Treatment of Haematemesis & Melaena:

- 1-General measures: See treatment of varices
- 2-Specific treatment: According to the cause
Lower GIT bleeding (see surgery \ dysentery)

ASCITES

Physiology:

- The normal peritoneal cavity contains about 100 ml of fluid
- It is a transudate and has a 50% turnover per hour
- It is produced by visceral capillaries.
- It is drained via diaphragmatic lymphatics

ASCITES: Accumulation of fluid in the peritoneal cavity.

Aetiology

1) Increased hydrostatic pressure: (Portal hypertension)

A) Post-sinusoidal (causes of cardiac cirrhosis = congested liver)

- Right-sided heart failure
- Tricuspid valve disease stenosis & incompetence
- Pericardial effusion & Constrictive pericarditis.
- Inferior vena cava obstruction
- Budd-Chiari syndrome
- Veno-occlusive disease

B) Sinusoidal:

- Liver cirrhosis: (for pathogenesis: see liver failure) (page 28)

C) Pre-sinusoidal: uncommon cause of ascites except if associated with hypoalbuminaemia-eg., PV thrombosis.

(Non-portal hypertension)

2) Hypoalbuminaemia:(Decreased colloid osmotic pressure)

1. End-stage liver disease (LCF)
2. Nephrotic syndrome (massive proteinuria)
3. Malnutrition
4. Protein-losing enteropathy

3) Increased permeability of peritoneal capillaries:(Peritoneal disease)

1. Infections:-

- Tuberculous peritonitis
- Bacterial peritonitis (secondary or SBP)

2. Tumours:

- Secondary malignancy
- Mesothelioma
- Pseudomyxoma peritonei

4) Leakage of fluid into the peritoneal cavity:

1. Bile ascites
2. Pancreatic ascites (secondary to a leaking pseudocyst)
3. Urine ascites
4. Chylous:
 - Obstruction of thoracic duct or abdominal lymphatics by tumours e.g. lymphomas.

- Rupture of abdominal lymphatics by trauma.
- Congenital malformations of lymphatics

5) Miscellaneous causes:

1. Myxedema
2. Ovarian disease (Meigs' syndrome)
3. Chronic hemodialysis
4. Haemorrhagic blood diseases
5. Trauma

Clinical Picture

A) **Symptoms:** May occur especially in tense ascites

D →	• Abdominal distension	• Abdominal discomfort
	• Dyspepsia (<i>early satiety</i>)	• Dyspnea (respiratory distress)
	• Development of abdominal hernia	

B) **Signs:**

Inspection:

Symmetrical distension of the abdominal contour, with fullness of the flanks (the most dependent)

In chronic cases there are:

- Widening of subcostal angle
- Divarication of recti
- Umbilicus is shifted downwards, everted & may be expansile with cough (umbilical hernia)
- Dilated veins on the abdominal wall may occur due to
- Portal hypertension (caput Medusae) or – IVC obstruction

Palpation:

1. Fluid thrill in tense ascites
2. Liver & spleen may be felt by dipping into tense ascites
3. Abdominal masses may be felt in malignancy & T.B.

Percussion:

1. Central resonance with dullness in the flanks & suprapubic area.
2. Shifting dullness is the most important clinical sign of ascites.
3. Mild ascites could be detected by finding dullness around the umbilicus in knee-elbow position.

Auscultation:

Venous hum may be heard over dilated & IVC obstruction

Puddle sign

C) Features of the Cause: e.g. generalized oedema in cases of hypoalbuminaemia.

D) The patient may presented by complications of ascites or extra-abdominal effect

Complication of ascites:

- Refractory
- Hepat-renal syndrome
- Spontaneous Bacterial Peritonitis SBP
- Complication of treatment (drugs or paracentesis)

Extra-abdominal effects of ascites:

- Pleural effusion: especially on the right side probably due to passage of fluid through defects in the diaphragm.
- Elevation of the diaphragm:
 - Decreased breath sounds & dullness on the bases of the lungs.
 - Displacement of cardiac apex upwards & outwards.
 - Congested pulsating neck veins
- May be swelling of the scrotum (hydrocele)

Investigations

(Images – fluid-detection of the cause – prediction of complication)

1. Abdominal ultrasound\CT: Sensitive methods to

- Detect presence of ascites even if minimal
- Differentiate free from encysted ascites.
- Help in detection of the cause eg., presence of cirrhotic liver

2. Aspiration of Ascitic fluid:

Ascitic fluid is examined for physical, chemical, cytological & bacteriological characters.

a. In exudates & transudate effusions:

	transudate	Exeudate
Proteins	<3 gm %	>3 gm%
Specific gravity	< 1016	> 1016
Cells (WBC)	< 1000/mm ³	>1000/cm ³
LDH	<200 IU/L	>200 IU/L

The serum-ascitic albumin gradient (S-AAG):- correlates with portal pressure

- S-AAG $\geq$ 1.1 g/di :- Portal hypertension (transudative ascites)
- S-AAG $\leq$ 1.1 g/di :- no portal hypertension (exudative ascites)

b. In exudates effusion:- the following findings are helpful

- Excess PNLs = infections.
- Excess lymphocytes = T.B. & lymphoma.
- Adenosine deaminase + Culture = for T.B.

c. Chylous effusion: The fluid is milky white, rich in fat, clears on addition of ether & stains orange with Sudan III.

d. Others: High amylase = pancreatic ascites.

3. Investigations for the cause: e.g.

- Liver function tests
- Laparoscopy & biopsy: may be needed e.g. in T.B. and malignancy.

Differential Diagnosis:

A) From other causes of abdominal swelling (5 Fs)

1. Fat = Obesity
2. Fetus = Pregnancy
3. Fluid = including cysts – Retention of urine
4. Flatus & Feces = IBS
5. Fibroid = Huge abdominal organomegaly or tumour e.g. ovarian cyst.

B) Differential Diagnosis of the Cause of Ascites: by using SAAG ratio

Treatment:

Treatment of ascites depends on its cause

Treatment of ascites in cirrhosis may precipitate or aggravate hepatic encephalopathy & renal failure. So, ascites should not be treated in patients with evidence of encephalopathy.

Treatment of cirrhotic ascites

1) Rest in bed: May lead to diuresis by improving renal perfusion.

2) Diet:

- Salt restriction
- Fluid restriction (if Na < 120 mmol/L)
- High protein diet is given. Proteins should be restricted if there is any evidence of encephalopathy.

..Patient without peripheral edema usually has weight loss of 0.5 Kg/day....

3) Follow up :

- Daily measurement of urine volume & body weight
- Monitoring of electrolytes (Na & K) and renal functions.

4) Diuretics:

- Indications: if weight loss is less than 1 kg after 4 days
- At first: Potassium-sparing diuretics e.g. spironolactone (100-400 mg/day) are used since they have mild action and cause potassium retention.
- No response: frusemide (40-120mg/day) or dihydrochloro-thiazide (25-100 mg/day) is added. Potassium supplements may be needed.
- Resistant cases: Osmotic diuretics as IV mannitol or Dopamine: 1-3 ug/kg/min IV infusion may be used.

5) Salt free albumin: only indicated in cases of advanced hypoalbuminaemia

Refractory Ascites:

Diuretic resistant: No response to the maximum dose of diuretics (400 mg of spironolactone and 160 mg of furosemide/day) or frequent ascites recurrence shortly after therapeutic paracentesis.

Diuretic intolerance: appearance of diuretics side effects as symptomatic hyponatremia, renal insufficiency or hepatic encephalopathy.

6) Therapeutic paracentesis:Indications:

- Resistant cases
- Tense ascites e.g. causing respiratory distress
- Impending rupture of umbilical hernia.

Avoided: in hepatic encephalopathy or renal failure

Technique: The volume aspirated must be about 4-8 liters at one time & it is better to be combined with administration of IV albumin (6 gm albumin must be given after each liter of fluid removed).

7) Treatment of resistant cases: resistance to treatment may be due to:

Defect	Treatment
Lack of salt restriction	Restrict salt restriction
Severe hypoalbuminaemia	IV salt-free albumin
Dilutional hyponatraemia	Fluid restriction, IV mannitol & dopamine
Secondary hyperaldosteronism	Spironolactone
Sever hypokalaemia	K supplementation and K-sparing diuretics
Local causes: SBP, TB or malignancies.	Specific treatment
Severe terminal cases	- Peritoneo-venous shunt - Ascites ultrafiltration & reinfusion - TIPS - Hepatic transplantation.

* Peritoneo-venous shunt: (as Le Vein shunt): A catheter is introduced from the peritoneal cavity to the SVC allowing passage of the ascetic fluid into the circulation – It may be complicated by hypervolaemia, pulmonary oedema, infection & DIC.

Spontaneous bacterial peritonitis

Def.: Form of peritonitis that occurs in patients with cirrhosis in the absence of a cause for peritonitis.

Incidence: 10-30% of hospitalized patients with ascites

Effect: can cause marked decompensation of the liver disease, with other complications and death occurring frequently.

Pathogenesis: diminished antibacterial activity of the ascetic fluid in cirrhotics. The infecting organisms are usually coliform bacteria (E coli) passed from the colon to the ascetic fluid transmurally

Clinical Picture:

1. Asymptomatic only diagnosed by paracentesis
2. Typical presentation: with fever and/or abdominal pain.
3. Atypical presentation: worsening of the encephalopathy or renal dysfunction

Investigations:-

Paracentesis: Polymorphonuclear (PMN) count of > 250 cells/uL.

Variant of SBP: Culture-negative neutrocytic ascites (must be treated as SBP)

Treatment: Cefotaxime (2 g IV every 8 hours for 5-days) a broad-spectrum, third-generation cephalosporin is the treatment of choice for SBP

Prophylaxis: Once patients have recovered from SBP, they require regular prophylactic antibiotics (Ciprofloxacin) as long as they still have ascites.

Malignant ascites

Aetiology:

1. Secondary to abdominal malignancy:- as ovaries, pancreas, colon
Spreading: Direct - lymphatic - haematogenous.
2. Secondary to extra-abdominal malignancy:- as cancer breast (rare)
3. Primary tumours e.g. mesothelioma (rare)

Clinical Picture:

1. Manifestations of the primary tumour
2. Malignant ascites is usually massive, rapid re-accumulated

3. Abdominal masses may be detected

4. Umbilical nodules may be present

Investigations:

Paracentesis:- Straw-coloured or bloody and may contain malignant cells.

Treatment:

- Intraperitoneal injection of cytotoxic drugs.
- Abdominal paracentesis may be needed in cases of tense ascites.

TUBERCULOUS PERITONITIS

Biological types:

- 1) Primary: occurs in children due to ingestion of infected milk. The bovine bacilli are the cause of infection in 80% of cases.
- 2) Secondary: due to reactivation of a tuberculous focus in the abdomen often a lymph node, tuberculous enteritis, & pulmonary tuberculosis.

Types:

1. Ascetic: free fluid in the peritoneum with no adhesions.
2. Loculated: adhesions divide the peritoneal cavity into many loculi.
3. Adhesive form: causing adhesions of the intestinal loops.

Clinical Picture:

Symptoms: Symptoms of TB toxemia

Constipation or diarrhea - Abdominal pain

Signs: Unilateral shifting dullness

Abdominal tenderness with mild rigidity of the abdomen

Palpable masses, (rolled omentum)

There is a doughy sensation on palpation of the abdomen

No lower limb edema

Complications:

- 1) Intestinal obstruction (adhesive)
- 2) Intestinal fistula
- 3) spread
- 4) amyloidosis

Investigations:

1. Abdominal sonar: Free or encysted ascites
2. Plain X-ray abdomen :- Calcified mesenteric L.N
3. CT and sonography: showing mesenteric thickening and lymph node
4. Laparoscopic examination for peritoneal tubercles and biopsy.
5. Tapping of the ascetic fluid: Straw-colored - Rich in proteins & lymphocytes plus Z.N., culture or PCR for the organism

Treatment: Antituberculous treatment.

Jaundice

DEFINITION: yellowish discolouration of the sclera, skin and mucous membranes, due to increased level of serum bilirubin. Which is better seen in sun light or UV *Jaundice is usually detectable when serum bilirubin exceeds 2.5-3 mg/dl*

Pathogenesis:

A)Haemolytic	B)Obstructive	C)Hepatocellular
RBCS → Hb → Bilirubin (indirect)↑	RBCS → Hb → Bilirubin (indirect)↑	RBCS → Hb → Bilirubin (indirect)↑
High stercho. & uro.	No stercho. Or uro.	Low stercho. & high uro.
✓ haemolysis of RBCs leads to increased haembilirubin. ✓ The liver can't uptake haembilirubin completely, so part of it is retained in the blood----> increased serum indirect bilirubin. ✓ A large part of haembilirubin is converted to cholebilirubin & excreteted by liver ----> increased stercobilinogen <u>Dark stools</u>. ✓ Increased stercobilinogen absorbed from intestine increased urobilinoge	✓ Decreased excretion of bilirubin into the intestines due to obstruction. ✓ Cholebilirubin regurgitates into the blood leads to 3 effects:- 1. Increased serum <u>direct bilirubin</u>. 2. Decreased bile excretion into the intestines --> <u>Steatorrhea</u> 3. Cholebilirubin appears in urine---> <u>Dark urine</u>. <i>Bile salts regurgitate into the blood & appear in urine.</i>	Hepatocytes dysfunction as:- 1. Defect in uptake and conjugation leads to rise of <u>indirect bilirubin</u> 2. Defect in excretion leads to rise of <u>direct bilirubin</u>. ✓ Stercobilinogen is secreated (<u>Pale stools</u>). ✓ Cholebilirubin & bile salts appear in urine (<u>Dark forthy urine</u>) ✓ Stercobilinogen absorbed to enter the enterohepatic circulation not entirely uptaken by the liver so excretated by the kidney as urobilinogen (<u>urobilinogen increased</u>)

- Urine is normal in colour in haemolytic jaundice except: with standing, during haemolytic crisis or if associated gall stones caused obstructive jaundice.

Aetiology:

Diseases	Causes of Obstructive jaundice <u>A- Extra-hepatic Obstruction:</u> 1. In the lumen: - Gall stones in the CBD -Worms as ascaris or fasciola. 2. In the wall: - Strictures: Congenital atresia, post-operative or inflammatory. – Tumours: as cholangiocarcinoma. 3. Pressure from outside: - Cancer head of pancreas. – Enlarged LN in porta hepatis. - Chronic pancreatitis. – Carcinoma of the ampulla of Vater. <u>B- Intra-hepatic Obstruction:</u> 1. Primary biliary cirrhosis. 2. Cholestatic jaundice of pregnancy. 3. Viral hepatitis (cholestatic type) 4. <u>Drugs</u> :androgens-oestrogen-chlorpromazine-tolbutamide. 5. Secondaries in the liver. 6. Chronic haemolytic anaemia. 7. Hereditary disorders:(no actual obstruction) (see below)	Causes of LCF 1. Infections: Viral hepatitis (CMV, herpes, EB-V, yellow fever). Septicaemia, multiple pyaemic abscesses. Leptospirosis, toxoplasmosis. 2. Drugs & toxins:- - Alcohol, halothane, isoniazid & paracetamol. - Carbon tetrachloride & D.D.T.-Atebrine.-Phosphorus. 3. Acute fatty liver of pregnancy. 4. Reye's syndrome. 5. Budd-Chiari syndrome. 6. Liver cirrhosis. 7. Chronic active hepatitis. 8. Terminal cases of obstructive jaundice. 9. Malignancy: e.g. metastases. 10. Lucey-Driscoll syndrome:- Inhibition of UGT by a substance in the maternal serum. 11. Breast milk Jaundice:- inhibition of UGT by a substance in the breast milk (free fatty acids or β -glucuronidase). 12. Hereditary diseases (see below)
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Clinical picture:

1. Jaundice is usually mild (lemon yellow) with dark stools & urine is normal in colour except. 2. Features of haemolytic anaemia. 3. Features of the cause e.g. thalassaemia.	1. Jaundice is usually deep (Olive green) with pale stools & dark frothy urine. 2. Other features of obstructive jaundice:- - Pruritus (bile salts are irritant to skin). - Bradycardia. - Bleeding tendency (improved after IV Vitamin K). - Bone affection:- osteoporosis & osteomalacia (hepatic osteodystrophy). - Steatorrhea (Pale, bulky, offensive & greasy stool). - Xanthomata (accumulation of cholesterol). 3. Features of the cause e.g. gallstones.	1. Jaundice is usually orange yellow with pale stools & dark urine. 2. Features of LCF may be present. 3. Features of the cause e.g. viral hepatitis.
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Investigations:**3x5 (5 lab, 5 imaging, 5 instrumental)****1. Laboratory investigations: Liver function tests:**

Excretory function			Liver damage		stercobilinogen	urobilinogen
	Unconjugated bilirubin	Conjugated bilirubin	SGOT & SGPT	Alk. phosphatase		
Hemolytic	↑ ↑	normal	normal	Normal	↑	↑
Hepatocellular	↑	↑ ↑	↑ ↑ ↑	↑	↓	↑
Obstructive	normal	↑ ↑	↑	↑ ↑ ↑	↓	↓

B- Images

<u>Ultrasound</u> <u>+/-CT</u>	-Hepatosplenomegaly	- Gall stone - Biliary system obstruction - Cancer head of pancreas	- Liver cirrhosis - liver tumours. - Spleen & portal vein - Ascites.
Abd. X ray Ba. swallow Ba. meal		- Gallstones - Pancreatic calcification. - Cancer head:- wide duodenal loop. - Cancer ampulla of Vater :- second part shows reversed number 3 deformity.	Oesophageal varices

Instrumental:

1- **ERCP**: Endoscopic Retrograde Cholangio- Pancreatography
Technique:- Visualization, cannulation of the ampulla of Vater then injection of dye.

Value: **diagnostic**:- Can detect the site & cause of obstruction (biliary or pancreatic)-

Therapeutic:- stone removal or biliary stent insertion

2- **PTC**: Percutaneous Trans-hepatic Cholangiography
Technique: visualization of the bile ducts by injection of dye through the liver.

3- **MRCP**: magnetic resonant Cholangio-Pancreatography.
Technique: visualization of the biliary and pancreatic ducts by MRI.

4- **Liver biopsy**: after correction of bleeding tendency
Technically difficult if ascites is present

5- **Laparoscopy**

Hereditary Hyperbilirubinemia:

Conjugated	Unconjugated
<u>Dubin-Johnson syndrome:</u> Hereditary defect in excretion of bile pigments with greenish-black liver & no pruritus.	<u>Gilbert's syndrome:</u> defect in the uptake & conjugation of bilirubin.
<u>Rotor syndrome:</u> resembles Dubin- Johnson syndrome with normal colour of the liver.	<u>C/P:-</u> Benign, with no liver change usually asymptomatic or present with mild intermittent jaundice increased with fasting <u>Crigler Najjar syndrome:-</u> congenital deficiency of the conjugating enzyme (2 types): <u>Type 1 (severe):-</u> Absent UGT – Fatal(Kernicterus) <u>Type II (mild):-</u> decreased UGT – mild jaundice.

Approach to patient with jaundice

Differential diagnosis of a case of jaundice

A) History Talking:**Personal History**Age:

- Children: haemolysis & viral hepatitis are more common.
- Adults: calculous obstruction & viral hepatitis are more common.
- Old age: malignant obstruction is more common

Sex:

- Calculous obstruction is more common in females.
- Malignant obstruction is more common in males.

Special habits: Alcohol may cause liver diseases e.g. cirrhosis.**History of present illness**

	O/C/D
Acute onset regressive for short duration	Hepatitis
Acute onset and intermittent	Calculous
Gradual onset progressive for short duration (months)	Malignancies
Gradual onset progressive for long duration (years)	Cirrhosis

Intermittent: (recurrent jaundice)

Calculous obstruction	Haemolysis	Chronic active hepatitis
Gilbert's disease	Benign cholestasis	Cancer ampulla of Vater

Analysis of jaundice:**(Colours + Ps = pain – pyrexia – pruritus-bleeding + GIT)**Colours of urine and stoolUrine: - Dark in obstructive & hepatocellular jaundice.

- Normal in haemolytic jaundice (except)

Stools: - Pale with features of steatorrhoea in obstructive jaundice.

- Usually pale in hepatocellular jaundice.
- Dark in haemolytic jaundice.

Pyrexia (Fever):

- In pre-icteric stage of viral hepatitis.
- Charcot's triad in calculous obstruction due to cholangitis (fever with rigors, jaundice & pain in right hypochondrium)
- During haemolytic crisis.
- Low – grade fever in cirrhosis & malignancy.

Pain:

- Biliary colic in calculous obstruction.

- Epigastric pain radiating to the back in cancer head of pancreas.
- Right hypochondrial and epigastric dull aching pain in viral hepatitis.
- Abdominal, back & bone pains in haemolytic crises.

Pruritus: - In obstructive jaundice.

Bleeding tendency: - In obstructive jaundice.

GIT: Anorexia, nausea & vomiting:

- Pre-icteric stage of hepatitis
- Calcular obstruction
- During haemolytic crises.
- Cancer head of pancreas.

Marked loss of weight in malignancies:

Past History

- Biliary colic or fatty dyspsia in calcular obstruction:
- *Drug:*
 - induced Intra-hepatic cholestasis.
 - Drug-induced hepatitis.
 - Drug-induced haemolysis.
 - Drug-abuse
- Blood transfusion.
- History of viral hepatitis or contact with cases of viral hepatitis

Family History

- Hereditary haemolytic anaemia.
- Gilbert's disease.
- Dubin-johnson & Rotor syndromes.

B) Physical Examination:-

General Examination

Colour of jaundice: (see table)

Manifestations of chronic haemolytic anaemia : (see haematology)

Manifestations of obstructive jaundice: (see table)

Manifestations of liver cell failure: (see hepatic failure)

Specific features:

- Cachexia in malignancies.
- Skin pigmentation & clubbing in primary biliary cirrhosis.
- Ecchymosis in hepatocellular & obstructive jaundice

- Oedema of lower limbs:
 - Liver cirrhosis & other causes of liver failure
 - Obstruction of inferior vena cava due to hepatic malignancy.

Abdominal Examination

Liver:

- Enlarged, soft & tender in viral hepatitis.
- Firm with sharp border & usually shrunken in cirrhosis.
- Enlarged, tender nodular in hepatic malignancy.
- May be enlarged in chronic haemolytic anaemia.

Splenomegaly:

- In haemolytic anaemias
- In liver cirrhosis & chronic active hepatitis.
- May/be in viral hepatitis.

Gall bladder: (Courvoisier's law)

- It is usually enlarged & palpable in malignant obstructive jaundice.
- It is usually tender & not palpable in calculous obstructive jaundice.

Ascites :

- Liver cirrhosis & other causes of liver failure
- Malignant infiltration of the peritoneum.

Signs of portal hypertension as caput medusa

Abdominal masses in malignancy.

II – Investigations: (see table)

AMOEBIC LIVER ABSCESS**Aetiology:**

- Infection with the the protozoan parasite *Entamoeba histolytica*
- The liver is the commonest extraintestinal site of infection
- haematogenous spread from the colon to the liver via the portal vein.
- Can present several years after intestinal infection (***Amoebic dysentery is present in only minority of cases***).
- It is more common in males.

Pathology:

- The abscess is usually solitary & most commonly situated in the upper part of the right lobe of the liver.
- The wall of the abscess is shaggy necrotic tissue contains chocolate-brown necrotic material.

Complications:

A) Spread & rupture: that may lead to

1. Subphrenic abscess
2. Pleurisy, pleural effusion or empyema
3. Basal consolidation or lung abscess
4. Amoebic pericarditis (with left lobe abscess)
5. Peritonitis
6. Cutaneous amoebiasis

B) Secondary pyogenic infection

C) Chronicity

D) Haematogenous dissemination: to lungs & brain.

Clinical Picture:

Symptoms: (fever + pain + complication)

Constitutional: Fever, headache, malaise, sweating & may be rigors.

Pain: Dull aching, stabbing, or throbbing pain.

- Felt in the right hypochondrium & lower chest and may be referred to the right shoulder & back.
- It is accentuated by coughing, stooping & straining and improves by leaning to the left side.

Symptoms of complications may be present 5% of patients.

Signs:

General:

Fever is usually mild or moderate. High fever occurs with secondary infection. It may be intermittent, remittent or continuous.
Pallor & toxic features

Jaundice is rare & if present it is due to bile duct obstruction by the abscess.

Local:

The liver is enlarged, soft & tender

Tenderness of the right lower ribs & intercostals spaces.

Rarely oedema of the skin of chest and abdominal wall may occur,

Signs of complications may be present.

<i>Investigations</i>			
Biochemical	Images	interventional	Others
Stool-CBC	Chest X-ray	Colonoscopy	Serological
LETs	U/SCtscan	Aspiration	Therapeutic test

1. Stool examination: vegetative form or cyst of EH may be found (rare).
2. Blood picture: Leucocytosis and may be normochromic anaemia.
3. Liver function tests: liver function tests: usually normal but alkaline phosphatase may be raised.
4. Chest X-ray & screen :-
 - Raised right hemidiaphragm
 - Pleural & pulmonary complications may be detected.
5. Abdominal ultrasound\CT scan: for diagnosis and localization of the abscess.
6. Colonoscopy or sigmoidoscopy: visualization and biopsy taken.
7. Diagnostic aspiration: better done under ultrasound guide: Anchovy – sauce fluid is aspirated in cases of amoebic abscess.
8. Serological tests: Latex agglutination assay (90%)-ELISA
9. Therapeutic test: Metronidazole is given & response is detected

Differential Diagnosis:

- Causes of enlarged tender liver
- Causes of fever with rigors
- FUO

Treatment

1. **General care:** Rest in bed with light nutrient diet
2. **Symptomatic treatment:** e.g. analgesics & antipyretics.
3. **Specific treatment**
 - I- Medical treatment: Amoebicidal Drugs
 1. **Metronidazole (Flagyl 1):** 750 mg t.d.s for 10 days.

2. **Tinidazole** (Fasigyn): 2gm daily for 5 days.
3. **Emetine hydrochloride**:- 1 mg/kg daily IM for 10 days.
Side effects: GI troubles – Hypotension – arrhythmias – heart failure-peripheral neuropathy.
4. **Dehydro-emetine**
5. **Chloroquine**

II- Needle aspiration: usually ultrasound guided aspiration
It may be indicated in cases not responding to medical treatment.

III- Surgical drainage: may be indicated in the following conditions.

- Cases not responding to medical treatment & aspiration.
- Huge abscess
- Left lobe abscess
- Multiple abscesses
- Secondary infection

4. Treatment of complications: e.g. antibiotics for secondary infection.

HEPATIC SCHISTOSOMIASIS

Aetiology:

- *Schistosoma mansoni* is responsible for most of the cases while *Schistosoma haematobium* is less common.
- In Egypt, the disease is more common in Delta region where *S. mansoni* is prevalent.
- It is more common in males, 10-40 years.

Pathogenesis:

- The bilharzial ova reach the liver via the portal system after failure to engage in the walls of the mesenteric & haemorrhoidal blood vessels.
- The ova induce cell-mediated immune response with formation of bilharzial granuloma in the portal tracts consists of ova surrounded by lymphocytes, macrophages, eosinophils & fibroblasts.
- Bilharzial granuloma healed by fibrosis leading to periportal fibrosis which may be:
 - Coarse periportal fibrosis (around the large portal veins)
 - Fine periportal fibrosis (around the small portal)
 - Mixed

Clinical Picture:

- Usually accidentally discovered by investigation
- Late features of portal hypertension may be present (see before)

- Bilharziasis is a pure periportal fibrosis without cirrhosis so features of liver failure only occurred if cirrhosis was coexisted.

Investigations:**1. Investigations for diagnosis of bilharziasis:**

- Stool & urine analysis: for schistosoma ova.
- Colonoscopy or sigmoidoscopy with rectal & colonic biopsy.
- Serological tests (ELISA, IF, COPT & CFT) and Skin test: may be false positive & may be positive because of an old infection.
- Liver biopsy: shows characteristic histological features of bilharzial granuloma and periportal fibrosis.

2. Investigations for portal hypertension: (see before)**3. Liver function tests:**

- Liver functions are usually normal in pure hepatic bilharziasis.
- However, chronic active hepatitis & post-hepatitis cirrhosis may be associated in many cases.
- Albumin may be decreased due to poor nutrition & repeated GI haemorrhage.
- Alkaline phosphatase may be raised.
- BSP test impaired

4. Liver imaging: e.g. abdominal ultrasonography & CT scan.**Treatment:**

1. Treatment of active bilharzial infection by antibilharzial drugs especially praziquantel.
2. Treatment of portal hypertension.
3. Antifibrotic drugs (e.g. colchicines) are of doubtful value.

FATTY LIVER

Definition: Excessive deposition of fat in the liver.

Aetiology:

Metabolic: Diabetes mellitus, Obesity, Abetalipoproteinemia, glycogen storage diseases acute fatty liver of pregnancy.

Nutritional: Malnutrition, total parenteral nutrition, severe weight loss, jejuno-ileal bypass, gastric bypass.

Drugs and toxins: alcohol, steroids, tetracycline, valproic acid, Amiodarone, methotrexate, diltiazem, tamoxifen.

Other:-Inflammatory bowel disease, HIV

Pathogenesis: (steatosis)

Microvesicular fatty change:- liver cells are filled with multiple fat droplets that do not displace centrally located nucleus.

Macrovesicular fatty change (late stages) the size of the vacuoles increases pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance.

Rarely, the disease may progress to steatohepatitis or even cirrhosis

Clinical Picture:

- Usually asymptomatic
- Liver is enlarged, soft with smooth surface & rounded edge.
- Acute fatty liver of pregnancy & Reye's syndrome may lead to acute liver failure.

Treatment:

- Treatment of the cause
- Low fat diet.
- Vitamins & lipotropics (of doubtful value)

HEPATIC TUMOURS

- Benign tumours: e.g. hepatocellular adenoma.
- Malignant tumours:
 - Primary e.g. hepatocellular carcinoma.
 - Secondary: more common than primary tumours.

Hepatocellular carcinoma (Hepatoma)

Age: usually over 40 years.

Sex: more frequent in males than females (3 : 1)

Predisposing factors:

- Cirrhosis: especially post-hepatitis cirrhosis & haemochromatosis
- Hepatitis B & C viruses
- Aflatoxin
- Androgens

HBV can predispose to hepatoma in either a cirrhotic or noncirrhotic liver by the integration of its DNA into the hepatocytes genom.

HCV:- Recently studies suggest that HCV is more common than HBV.

Alcoholics:- not common, unless has coexisting viral hepatitis.

Clinical Picture:**Symptoms:**

1. Abdominal pain with marked weight loss.
2. In cirrhotic patient:- HCC is expected if the patient rapidly developed:-
 - Rapid weight loss
 - An enlarging liver with a mass
 - Abdominal pain
 - Bloody ascites
 - Rapid deterioration of condition with ascites or encephalopathy.
3. May be accidentally discovered by ultrasound\ CT and or markers

Signs:-

General signs: - Cachexia - Low-grade fever
- Jaundice may be present.

Abdominal signs:

- The liver is enlarged, hard, irregular or nodular & tender.
- A bruit & a hepatic rub may be heard.
- Ascites may be present (usually bloody)

Metastatic manifestations (rare): e.g. in LNs, lungs, bones or brain.

Systemic non-metastatic manifestations (Paramalignant syndromes)
e.g. gynaecomastia, hypercalcaemia, hypoglycaemia & erythrocytosis.

Investigations: (images-tumour markers – biopsy)**Images:**

Abdominal ultrasound – CT scan – MRI – isotopic scan – angiography

Recently dynamic images used as triphasic CT scan.

Tumour markers:

Alpha fetoprotein: Normally less than 20 mg/ml

Marked elevation > 500 ng/ml are highly suggestive of hepatoma.

Mild or moderate elevation occurs in: malignancy of GIT, ovary & testis – hepatitis & cirrhosis (Alpha fetoprotein is pr-inflammatory marker).

Diagnostic criteria:-

Focal lesion > 2cm by U/S **plus** Alpha fetoprotein > 200 Ng

Liver biopsy: better done under ultrasound or CT guide.

Treatment:

1. Prophylaxis:- Screening strategies include ultrasound and/or a-fetoprotein determinations every 6 months in high-risk patients.

2. Surgical

Resection:- only about 25% patients are suitable for surgery.

Hepatic transplantation: curative in only a minority of patients.

3. Others:-

Chemotherapy: using adriamycin or mitozantrone.

Interventional :- Hepatic artery embolization or ligation (Cryotherapy- Thermotherapy)

Median survival in non-resectable disease is 6 months

DRUG-INDUCED LIVER DISEASE**Acute hepato-cellular injury**

1- Toxic necrosis: CC14 - acetaminophen (Dose-related lysis of hepatocytes)

2- Hepatitis-like: isoniazid-methyldopa (Idiosyncrasy $\pm$ immune)

Cholestasis

1- Inflammatory: chlorpromazine (Periportal inflammation and cholestasis)

2- Pure: oral contraceptives (Pure cholestasis, no inflammation)

Chronic liver disease

1-Chronic hepatitis: isoniazid - methyldopa (Idiosyncrasy $\pm$ immune)

2- Fibrosis/cirrhosis: methotrexate + Causes of ch. Hepatitis. (Dose-related, toxic\ metabolic damage)

3- Tumor: adenomas: Oral contraceptives (Unknown)

Fatty liver (steatosis) (see above): alcohol, steroids, tetracycline, valproic acid

Hepatobiliary reactions to oral contraceptives:

-Cholestasis -Tumors -Adenomas -HCC (rare) - Gallstones

-Focal nodular hyperplasia -Budd -Chiari syndrome (increased clotting tendency)

LIVER TRANSPLANTATION

The first human liver transplant was performed in 1963

Indications:

End-stage liver disease: cirrhosis, Budd-Chiari syndrome.

Fulminant liver failure

Hepatic malignancy

Metabolic diseases: Wilson's disease, haemochromatosis.

Biliary diseases: Biliary atresia, sclerosing cholangitis.

Contraindications:

- Systemic sepsis
- Metastatic malignancy
- AIDS (+/-)
- Portal vein thrombosis
- Severe cardiopulmonary disease

Modes of grafting:

- Orthotopic transplantation
- Heterotopic transplantation
- Split liver transplantation:- usually from son/only died cadaver

Recent:

Living donor liver transplantation (LDLT):

- A piece of healthy liver is surgically removed from a living person and transplanted into a recipient.
- 55% of the liver (the right lobe) is removed from a healthy living donor
- The donor's liver will regenerate to 100% function within 4-6 weeks.

Immunosuppressive management:

- Corticosteroids
- Calcineurin inhibitor such as tacrolimus or Cyclosporin
- Antimetabolite such as Mycophenolate Mofetil

Complications:

- Graft non-function
- Rejection
- Infections e.g. CMV
- Recurrence of the original disease

LIVER ENLARGEMENT**I- Liver Inflammation:*****A) Infections:*****1. Viral:**

- Viral hepatitis
- Infectious mononucleosis
- CMV, herpes simplex

2. Bacterial:

- Pyaemic abscesses
- Brucellosis
- Military T.B.
- Relapsing fever
- Typhoid
- Syphilis (congenital, 2ry & 3ry)
- Leptospirosis

3. Protozoal:

- Amoebic liver abscess
- Malaria
- Kala-azar
- Toxoplasmosis

4. Helminthes:

- Bilharziasis
- Hydatid cyst cyst
- Fasciola

B) Chemicals: e.g. Alcoholic hepatitis

C) Chronic hepatitis:

- Chronic active hepatitis
- Chronic persistent hepatitis

II- Liver Congestion:

- Right ventricular failure
- Tricuspid valve disease (stenosis & incompetence)
- Pericardial effusion & constrictive pericarditis.
- High inferior vena cava obstruction
- Budd-Chiari syndrome
- Veno-occlusive disease.

III- Liver Tumours:

- Primary:

- Benign e.g. hepatocellular adenoma
- Malignant e.g. hepatocellular carcinoma.
- Secondaries

IV-Liver Cirrhosis:

- Cardiac & Biliary cirrhosis
- Early stages of other causes of cirrhosis.

V- Obstructive jaundice: especially extrahepatic obstruction**VI-Haematological Diseases:**

- Megaloblastic anaemia
- Lymphomas
- Myelofibrosis
- Leukaemias especially CML.
- Polycythaemia vera

VII- Metabolic Diseases:

- Fatty liver
- Wilson's Disease
- Haemochromatosis
- Amyloidosis
- Lipid Storage Diseases: e.g. Gaucher's disease, Neimann-Pick disease.
- Glycogen Storage Disease e.g. Von Geirke's disease
- Galactosaemia

VIII- Miscellaneous:

- Collagen diseases e.g. SLE.
- Granulomatous diseases e.g. Sarcoidosis
- Inflammatory bowel disease